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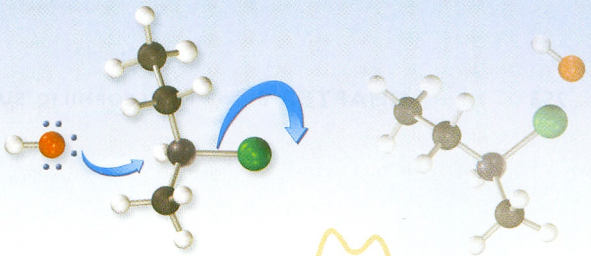

Nucleophilic Substitution Reactions

REACTIONS OF ALKYL HALIDES, ALCOHOLS, AND RELATED COMPOUNDS

CHAPTER 8

THIS CHAPTER provides our first detailed discussion of an organic reaction. In this reaction, a group attached to a carbon is replaced by another group. A simple example of this reaction is

$$HO^- + Cl{-}CH_3 \longrightarrow HO{-}CH_3 + Cl^-$$

This reaction is very important and useful because it enables us to exchange one group bonded to carbon (the Cl in this example) with another (the OH). The reaction is examined in considerable detail, using many of the same concepts that were introduced in Chapter 4 to help understand acid–base reactions.

The following features of this reaction are discussed:

- The two basic pathways, or mechanisms, by which the reaction occurs
- The stereochemistry of the reaction, that is, what happens when the carbon is a chirality center
- How other groups on the carbon affect the reaction
- Other groups that can be used in place of chloride ion or hydroxide ion in the reaction
- Competing reactions

In Chapter 9 the competing reactions are examined in more detail. Then, in Chapter 10, applications of these reactions to the preparation or synthesis of other compounds are presented.

MASTERING ORGANIC CHEMISTRY

- Learning the Two Mechanisms by Which Substitution Reactions Occur
- Recognizing Nucleophiles and Leaving Groups and Understanding the Factors That Control Their Reactivities
- Understanding the Factors That Control the Rates of Substitution Reactions
- Predicting Which Mechanism Will Occur for a Particular Reaction
- Predicting the Products of Substitution Reactions
- Predicting the Stereochemistry of the Products
- Recognizing When a Rearrangement Reaction Will Occur
- Recognizing the Products *Formed* from Competing Reactions

8.1 THE GENERAL REACTION

Let's examine the reaction of chloromethane with hydroxide ion in detail. We say that hydroxide ion has substituted for chlorine on the methyl group, so this type of reaction is termed a substitution reaction.

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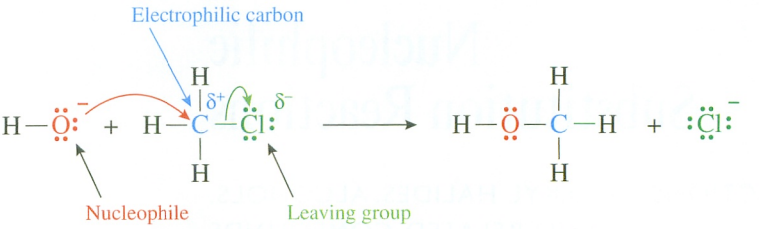
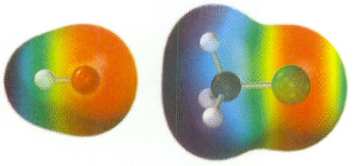




In this substitution reaction, the hydroxide ion is acting as a Lewis base, using one of its unshared pairs of electrons to form a bond to the carbon, which is reacting as the Lewis acid part of a Lewis acid–base complex. Therefore, these substitution reactions can be viewed as Lewis acid–base reactions. In reactions where carbon is involved, organic chemists have special terms for the Lewis acid and base. The Lewis base is called a **nucleophile,** which is derived from Greek words meaning "nucleus loving." A nucleophile is an electron-rich species that seeks an electron-poor site. The nucleophile can use a pair of its electrons to form a bond to this electron-deficient site. The Lewis acid is called an **electrophile,** which is derived from Greek words meaning "electron loving." An electrophile is an electron-poor species that seeks an electron-rich site, a nucleophile. The electrophile can accept a pair of electrons from the nucleophile and form a bond to it. In the preceding reaction, hydroxide ion is the nucleophile and CH_3Cl is the electrophile. To be more specific, the oxygen is the nucleophilic atom of hydroxide ion. The carbon of CH_3Cl is electron deficient due to the polarization of the carbon–chlorine bond, and it is the electrophilic atom. In the reaction, the nucleophile is attracted to the electrophile, and ultimately a bond forms between the nucleophilic atom and the electrophilic atom. To avoid exceeding the valence of the carbon, the chlorine must depart, taking the electrons of the carbon–chlorine bond with it. The chlorine is called the **leaving group.** The electrostatic potential maps of the reactants in the preceding reaction show electron-rich regions (nucleophilic sites) in red and electron-poor regions (electrophilic sites) in blue.

The concept of nucleophiles and electrophiles is one of the most important in organic chemistry. The reactions in this chapter, as well as most of the reactions that we will study in later chapters, involve a nucleophile bonding to an electrophile. If you can examine a molecule and identify whether it has a nucleophilic or an electrophilic site, not only will you know where that molecule is likely to react but you will also be able to identify what kind of partner is needed for a reaction because nucleophiles react with electrophiles.

Because the nucleophile replaces the leaving group, this type of reaction is termed a **nucleophilic substitution reaction.** A more general equation for a nucleophilic substitution reaction is

where Nu^- represents a general nucleophile and R—L represents a general leaving group (L) bonded to a carbon group (R).

8.2 Reaction Mechanisms

As introduced in Chapter 4, a reaction mechanism shows how the nuclei and the electrons move and how the bonds change as the reaction proceeds. It shows the individual steps in a reaction—that is, the order in which the bonds are made and broken. For example, the nucleophilic substitution reaction involves breaking one bond, the bond between the carbon and the leaving group, and forming one bond, the bond between the nucleophile and the carbon. There are three possible timings for these events—three possible mechanisms: (1) the bond to the leaving group may be broken first, followed by formation of the bond to the nucleophile; (2) the bond to the nucleophile may be formed first, followed by breaking the bond to the leaving group; or (3) bond breaking and bond formation may occur simultaneously. Pathways (1) and (3) both occur. Mechanism (2) does not occur, because the intermediate that would form when the nucleophile bonds first has five bonds to the carbon and cannot exist because the valence of the carbon would be exceeded.

Although certain mechanisms for a reaction can be eliminated on the basis of experimental evidence, it is never possible to prove that the reaction follows a particular mechanism. It can only be demonstrated that all the experimental facts are consistent with that mechanism. One piece of experimental information that is of primary importance is the rate law that the reaction follows. The rate law predicted by a possible mechanism must be consistent with the rate law determined in the laboratory. If the two are not consistent, that mechanism can be ruled out. In the case of these nucleophilic substitution reactions, experimental studies have shown that two different rate laws are followed, depending on the substrate (R—L), the nucleophile, and the reaction conditions. This means that there must be two different mechanisms for the reaction. Let's look at each.

8.3 Bimolecular Nucleophilic Substitution

Consider the reaction of hydroxide ion with chloroethane:

$$HO^- + CH_3CH_2{-}Cl \longrightarrow CH_3CH_2{-}OH + Cl^-$$

Investigation of this reaction in the laboratory has shown that the reaction rate depends on the concentration of hydroxide ion and on the concentration of chloroethane (EtCl), that is, the reaction follows the second-order rate law:

$$\text{rate} = k[\text{EtCl}][\text{OH}^-]$$

From general chemistry you might recall that the dependence of the rate law on the concentration of a particular species requires that species to be involved in the slowest step of the reaction or a step before the slowest step. Therefore, in this case, both hydroxide ion and chloroethane must be present in the slowest step of the reaction.

This rate law is consistent with mechanism (3), in which the bond to the leaving group (chloride) is broken and the bond to the nucleophile (hydroxide) is formed simultaneously, in the same step. A reaction that occurs in one step is termed a **concerted reaction.** Because two species (hydroxide ion and chloroethane) are involved in this step, the step is said to be bimolecular. This reaction is therefore described as a **bimolecular nucleophilic substitution** reaction, or an $\mathbf{S_N2}$ reaction.

Diagrams that show how the free energy changes as a reaction proceeds were introduced in Chapter 4 and are very useful. Figure 8.1 shows such a diagram for the S_N2 reac-

tion. Recall that the free energy, G, of the system is shown on the y-axis in these diagrams, and the progress of the reaction, which is just a measure of how much the reaction has proceeded from reactants toward products, is shown along the x-axis. The reactants are shown on the left-hand side of the diagram and the products on the right-hand side.

In this case the products are lower in energy than the reactants, so $\Delta G°$ is negative (the reaction is **exergonic**). Such reactions proceed spontaneously to the right. (Reactions in which the free-energy change is positive are **endergonic** and are not spontaneous. The terms **exothermic** and **endothermic** refer to reactions in which the enthalpy change [$\Delta H°$] is negative and positive, respectively.)

Of more importance in terms of the mechanism is what happens to the energy of the system as the reaction progresses from the reactants to the products. As the reaction starts, the bond to the chlorine begins to break and the bond to the hydroxide ion begins to form. Initially, breaking the bond costs more energy than is returned by forming the other bond, so the energy of the system increases. The energy of the system continues to increase until it reaches a maximum where both bonds are approximately half formed (or broken). The structure of the complex at this energy maximum is called the **transition state.** Then the energy begins to drop as the energy decrease from forming the new bond outweighs the energy increase from breaking the bond to the leaving chlorine. The energy difference between the transition state and the reactants is the **free energy of activation,** $\Delta G^{\ddagger}$.

The free energy versus reaction progress diagram shown in Figure 8.1 is typical for a concerted reaction. There is only one energy maximum; there is one transition state, between reactants and products; and there is no minimum between them.

What does the transition state for the S_N2 reaction look like? Because it is a maximum on the free energy versus reaction progress diagram and any change, either forward to products or backward to reactants, is downhill in energy, the transition state has no appreciable lifetime. Because of this, it cannot be observed directly and any information

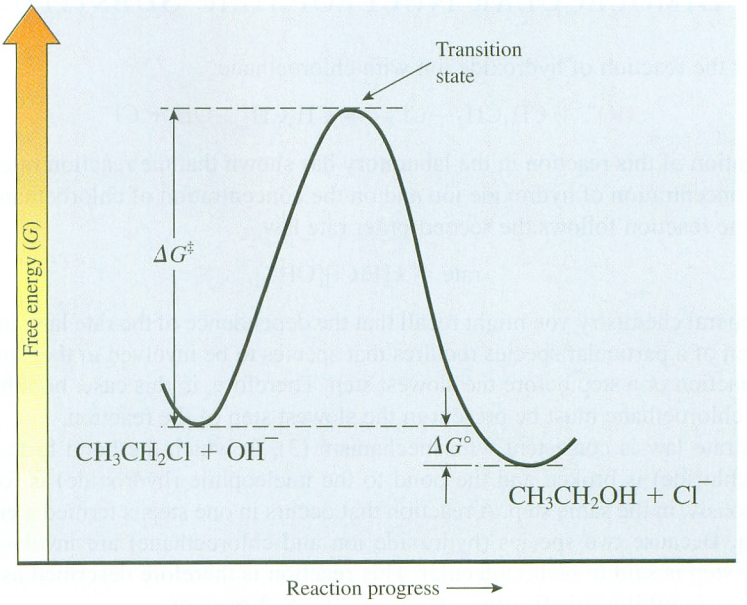


Figure 8.1

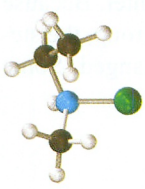
FREE ENERGY VERSUS REACTION PROGRESS DIAGRAM FOR THE S_N2 REACTION OF CHLOROETHANE AND HYDROXIDE ION.

about its structure must be obtained by indirect means. However, we do know that the transition state must have a five-coordinate carbon—that is, a carbon with five bonds: three normal bonds and two partial bonds. The geometry of these bonds in the transition state has been determined by investigation of the stereochemistry of the reaction.

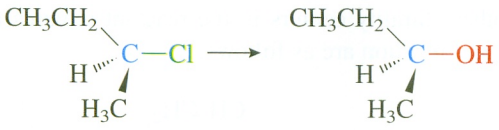
8.4 STEREOCHEMISTRY OF THE S_N2 REACTION

What happens in the S_N2 reaction if the leaving group is attached to a carbon that is a chirality center, that is, one that is bonded to four different groups (the leaving group and three other, different groups)? *Possible* stereochemical outcomes are illustrated in Figure 8.2 for the reaction of hydroxide ion with (*S*)-2-chlorobutane. In possibility 1 the product has the same relative configuration as the reactant. In such a case we say that the reaction has occurred with **retention of configuration.** In possibility 2 the product has the opposite relative configuration to the reactant. In this case the reaction has occurred with **inversion of configuration.** In possibility 3, complete randomization of stereochemistry has occurred in the product. The reaction has occurred with **racemization,** or 50% inversion and 50% retention. (Of course, partial racemization, resulting in different ratios of inversion to retention, is also possible.)

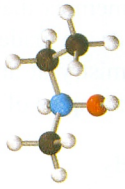
When the reaction of 2-chlorobutane with hydroxide ion is run in the laboratory, the rate is found to depend on the concentration of both species. This indicates that the re-



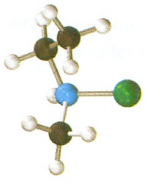
Possibility 1: Retention of Configuration



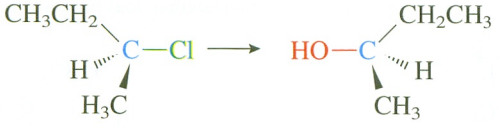
(*S*)-2-Chlorobutane (*S*)-2-Butanol



The hydroxide has bonded in the exact position the chlorine originally occupied. The product has the same relative stereochemistry as the reactant. The reaction has occurred with retention of configuration.



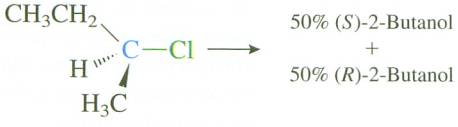
Possibility 2: Inversion of Configuration



(*S*)-2-Chlorobutane (*R*)-2-Butanol

The hydroxide has bonded to the side opposite that where the chlorine was originally bonded. The stereochemistry of the product is opposite that of the reactant. The reaction has occurred with inversion of configuration.

Possibility 3: Racemization



(*S*)-2-Chlorobutane

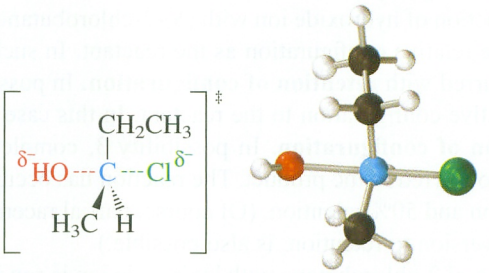
The hydroxide has bonded equally to the same side and the opposite side as the original chlorine. A complete loss of stereochemistry has occurred. The reaction has proceeded with racemization.

Figure 8.2

***POSSIBLE* STEREOCHEMICAL OUTCOMES FOR THE REACTION OF (*S*)-2-CHLOROBUTANE WITH HYDROXIDE ION.** Only possibility 2 actually occurs.

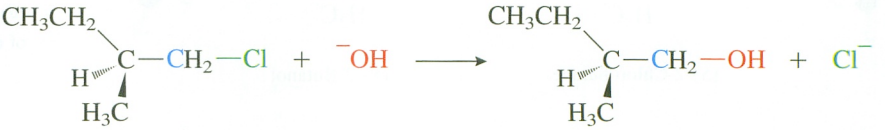
action is following the S_N2 mechanism. Investigation of the stereochemistry of the reaction shows that the product is formed with inversion of configuration; that is, (*S*)-2-chlorobutane produces (*R*)-2-butanol, corresponding to possibility 2 in Figure 8.2. The same result has been found for all S_N2 reactions. S_N2 reactions occur with inversion of configuration at the reaction center.

The fact that S_N2 reactions *always* occur with inversion of configuration enables us to form a better picture of the transition state. The nucleophile must approach the carbon from the side opposite the leaving group **(back-side attack).** The structure of the transition state, with partial bonds to the entering hydroxide and the leaving chloride, is shown in the following structure. Figure 8.3 uses orbitals to show how this process occurs.

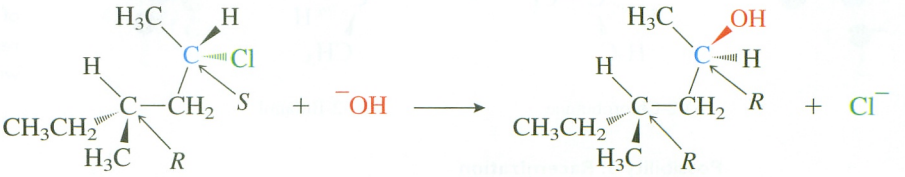


S_N2 transition state

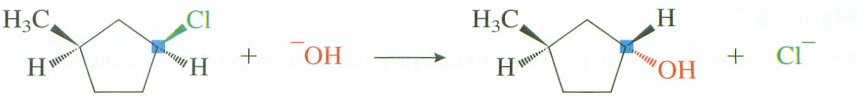
Remember that the stereochemistry is inverted only at the reaction center. Because no bonds are made or broken except at the carbon bonded to the leaving group, the stereochemistry at any other chirality centers in the reactant remains unchanged. Some more examples of the S_N2 reaction are as follows:

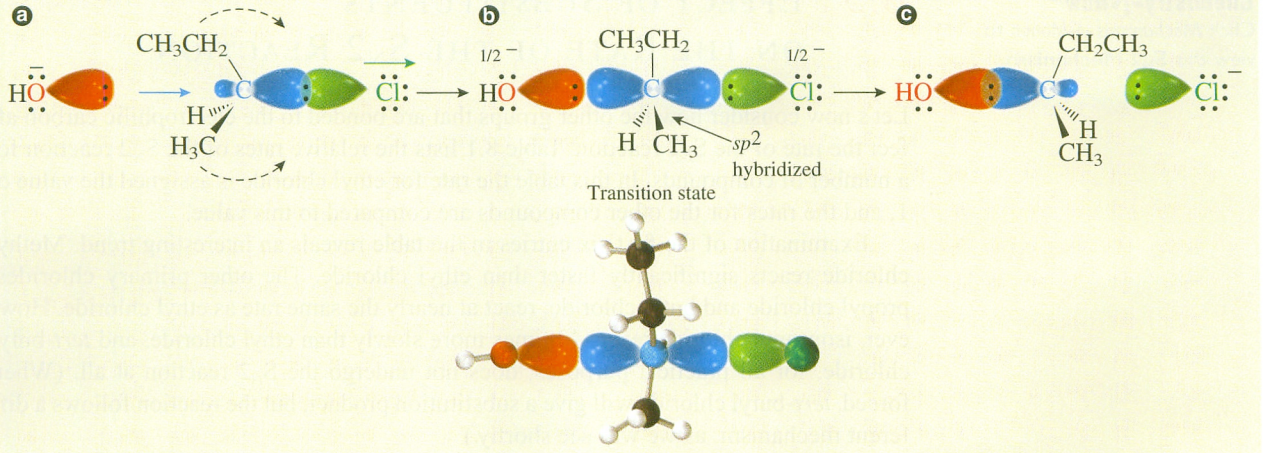


There is no change in the stereochemistry because the reaction does not involve the chirality center.



Stereochemistry is inverted at the reaction center; there is no change in the stereochemistry at the other chirality center because it is not involved in the reaction. The next example is similar.





a The nucleophile approaches the carbon from the side opposite the leaving group (back-side attack). An atomic orbital on the nucleophile, containing an unshared pair of electrons, begins to interact with the back lobe of the sp^3 orbital used by the carbon to form the sigma bond to the leaving group. As the nucleophile continues to approach, the leaving group begins to move away from the carbon, and the three other groups begin to swing to the right as the hybridization of the carbon changes.

b At the transition state, the carbon has trigonal planar geometry and is sp^2 hybridized. The AO of the nucleophile overlaps with one lobe of the *p* orbital on the carbon, and the AO of the leaving group overlaps with the other lobe of this orbital. The overall geometry is trigonal bipyramidal, with partial bonds to both Nu and L and approximate charges of negative 1/2 on each.

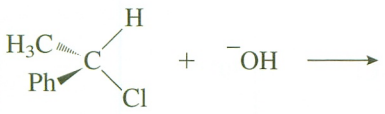
c As the nucleophile continues to approach, the distance between the carbon and the leaving group continues to increase, and the other three groups continue to swing to the right. The hybridization of the carbon changes back to sp^3, and its geometry returns to tetrahedral but with the nucleophile bonded to the side opposite to the one to which the leaving group was originally bonded.

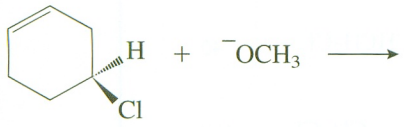
Active Figure 8.3 ORGANIC Chemistry Now™

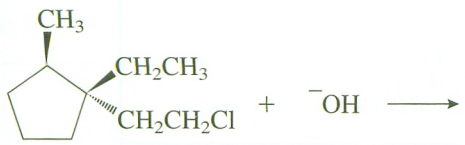
MECHANISM OF THE S_N2 REACTION OF (*S*)-2-CHLOROBUTANE AND HYDROXIDE ION SHOWING ORBITALS. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

PROBLEM 8.1

Show the products, including stereochemistry, of these S_N2 reactions:

a) 

b) 

c) 

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Click *Mechanisms in Motion* to view this **S_N2 Mechanism.**

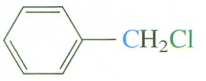
8.5 Effect of Substituents on the Rate of the S_N2 Reaction

Let's now consider how the other groups that are bonded to the electrophilic carbon affect the rate of the S_N2 reaction. Table 8.1 lists the relative rates of the S_N2 reaction for a number of compounds. In this table the rate for ethyl chloride is assigned the value of 1, and the rates for the other compounds are compared to this value.

Examination of the first six entries in the table reveals an interesting trend. Methyl chloride reacts significantly faster than ethyl chloride. The other primary chlorides, propyl chloride and butyl chloride, react at nearly the same rate as ethyl chloride. However, isopropyl chloride reacts 40 times more slowly than ethyl chloride, and *tert*-butyl chloride, for all practical purposes, does not undergo the S_N2 reaction at all. (When forced, *tert*-butyl chloride will give a substitution product, but the reaction follows a different mechanism, as we will see shortly.)

You can see that the rate of the S_N2 reaction decreases dramatically each time one of the hydrogens on the electrophilic carbon of methyl chloride is replaced with a

Table 8.1 Relative Rates of S_N2 Reactions for Selected Compounds

Name	Structure	Relative Rate
Methyl chloride	CH_3Cl	30
Ethyl chloride	CH_3CH_2Cl	1
Propyl chloride	$CH_3CH_2CH_2Cl$	0.4
Butyl chloride	$CH_3CH_2CH_2CH_2Cl$	0.4
Isopropyl chloride	CH_3CHCl (CH$_3$ branch)	0.025
tert-Butyl chloride	CH_3CCl (two CH$_3$ branches)	0
Neopentyl chloride	CH_3CCH_2Cl (two CH$_3$ branches)	10^{-5}
Allyl chloride	$CH_2{=}CHCH_2Cl$	40
Benzyl chloride		120
Chloroacetone	$CH_3C(=O)CH_2Cl$	10^5

methyl group. Thus, replacing one hydrogen with a methyl group, to give ethyl chloride, causes the rate to decrease by a factor of 30. Replacing a second hydrogen with a methyl, to give isopropyl chloride, results in a further rate decrease by a factor of 40. By the time three methyl groups have been added, to give *tert*-butyl chloride, the compound is unreactive in the S_N2 reaction. This effect is a result of the larger size of the methyl group (or other carbon groups) as compared to the size of hydrogen—a **steric effect.** The steric effect is a result of increasing strain energy in the transition state as the size of the groups on the electrophilic carbon increases.

Figure 8.4 illustrates this effect. It shows free energy versus reaction progress diagrams for the S_N2 reactions of methyl chloride, ethyl chloride, and isopropyl chloride with hydroxide ion. In the case of methyl chloride, very little steric strain is introduced into the transition state by the interaction of the hydroxide ion nucleophile with the hydrogens. In the case of ethyl chloride, the interaction between the nucleophile and the methyl group on the electrophilic carbon generates more steric strain in the transition state, causing it to increase in energy. This results in an increase in $\Delta G^{\ddagger}$ and slows the reaction. In the case of isopropyl chloride, the interaction of the nucleophile with two methyl groups causes even more steric strain in the transition state and slows the reaction even more. When three methyl groups are present, as in the case of *tert*-butyl chloride, so much strain is present in the transition state that the rate of the S_N2 reaction is extremely slow.

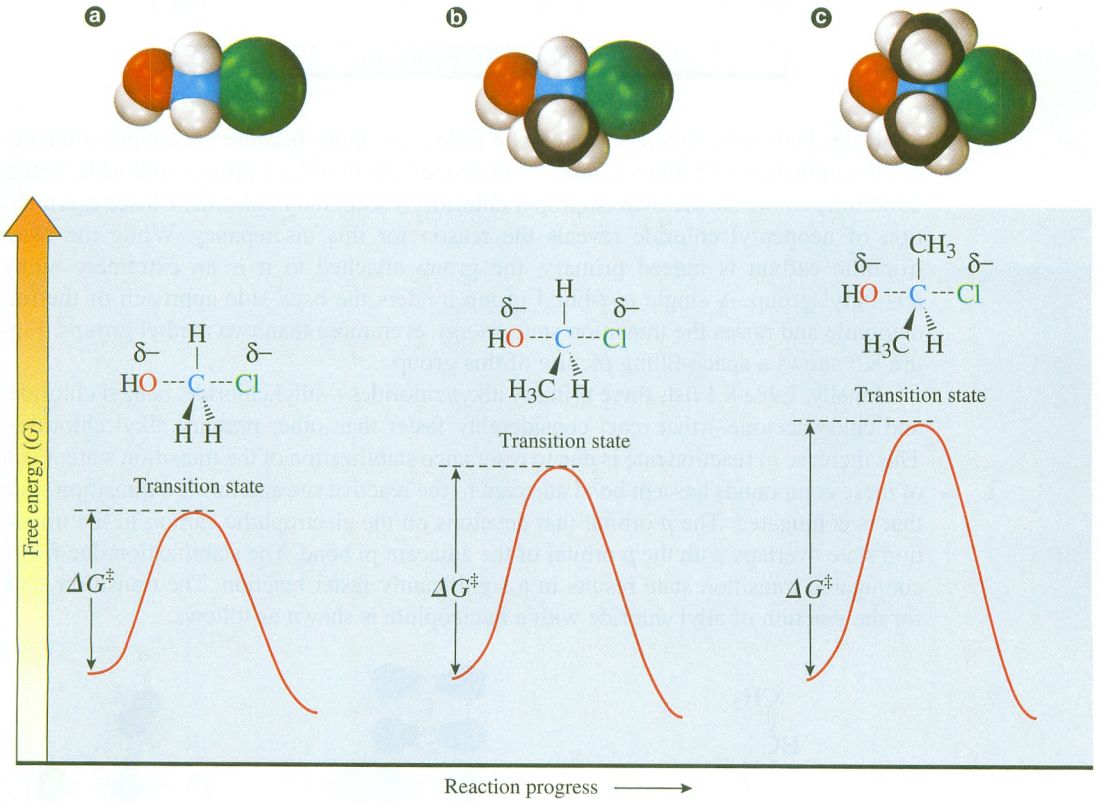


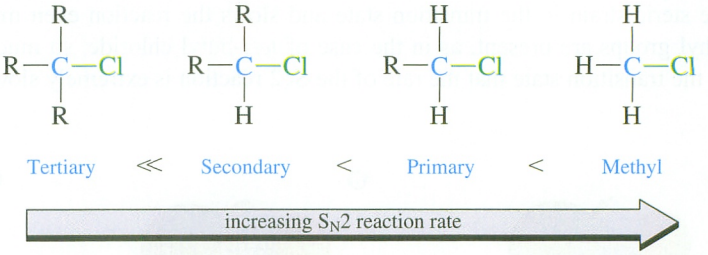
Figure 8.4

FREE ENERGY VERSUS REACTION PROGRESS DIAGRAMS FOR THE S_N2 REACTIONS OF (a) METHYL CHLORIDE, (b) ETHYL CHLORIDE, AND (c) ISOPROPYL CHLORIDE WITH HYDROXIDE ION.

Figure 8.5 provides another view of this effect. It shows computer-generated space-filling models of some of the molecules from Table 8.1 and illustrates the increasing difficulty the nucleophile experiences when approaching the back side of the electrophilic carbon and reaching the transition state as the number of methyl groups bonded to that carbon increases.

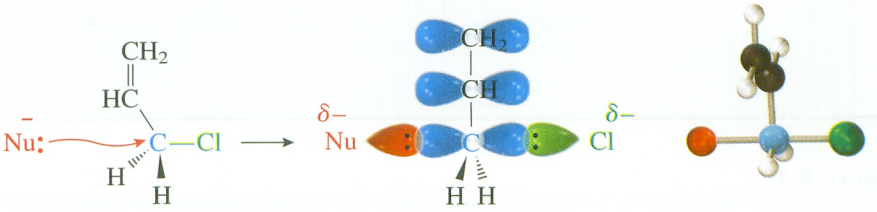
Other primary alkyl groups have effects similar to that of the methyl group. Replacing a hydrogen on the electrophilic carbon of methyl chloride with an ethyl group rather than a methyl group causes only a slightly larger rate decrease (compare the relative rates of ethyl chloride and propyl chloride in Table 8.1). This indicates that, as far as this mechanism is concerned, an ethyl group is only slightly "larger" than a methyl group, a result that is consistent with the axial destabilization energies of these groups discussed in Chapter 6.

To summarize, the rate of the S_N2 reaction is controlled by steric factors at the electrophilic carbon. Steric hindrance slows the reaction. Based on the number of carbon groups attached to that carbon, the reactivity order is



Rules in organic chemistry cannot be followed blindly, because exceptions often occur. Examination of Table 8.1 shows that neopentyl chloride, a primary chloride, reacts 2500 times more *slowly* than isopropyl chloride, a secondary chloride. Closer examination of neopentyl chloride reveals the reason for this discrepancy. While the electrophilic carbon is indeed primary, the group attached to it is an extremely bulky *tert*-butyl group. A single *tert*-butyl group hinders the back-side approach of the nucleophile and raises the transition state energy even more than two methyl groups. Figure 8.5 shows a space-filling picture of this group.

Finally, Table 8.1 lists three primary alkyl chlorides—allyl chloride, benzyl chloride, and chloroacetone—that react considerably faster than other primary alkyl chlorides. This increase in reaction rate is due to resonance stabilization of the transition state. Each of these compounds has a pi bond adjacent to the reactive site and forms a transition state that is conjugated. The *p* orbital that develops on the electrophilic carbon in the transition state overlaps with the *p* orbital of the adjacent pi bond. The stabilization due to the conjugated transition state results in a significantly faster reaction. The transition state for the reaction of allyl chloride with a nucleophile is shown as follows:



3-Chloro-1-propene (allyl chloride) Transition state

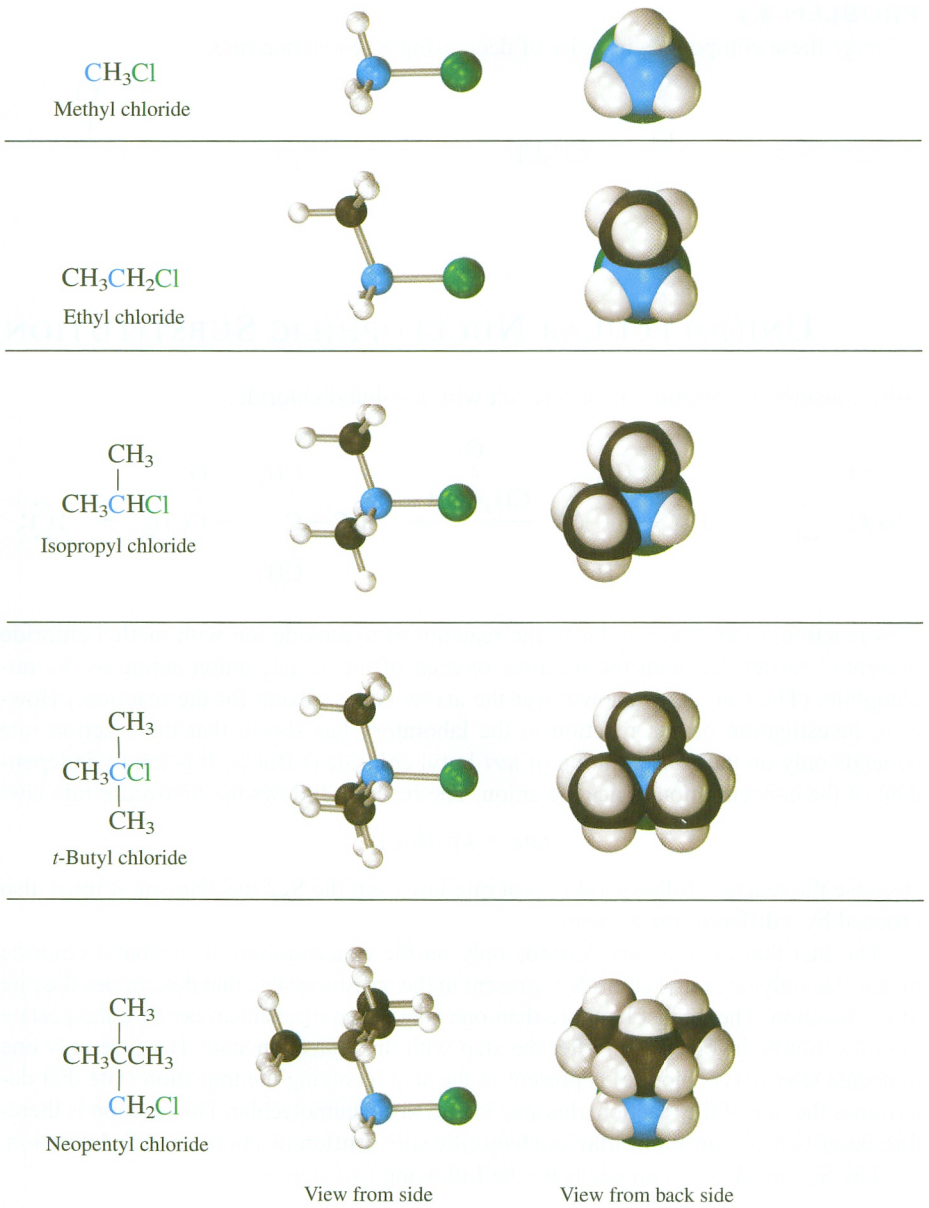
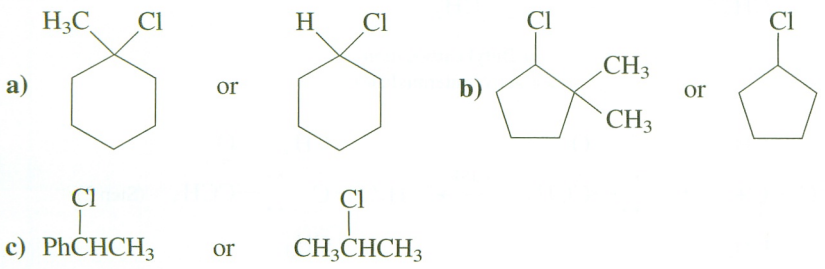


Figure 8.5

SOME ALKYL CHLORIDES. Chlorine is green, and the electrophilic carbon is blue.

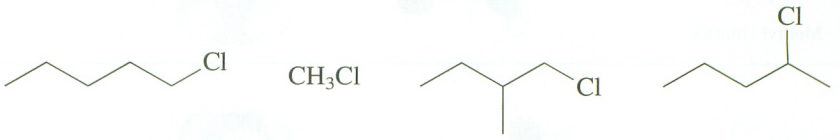
PROBLEM 8.2

Explain which compound has a faster rate of S_N2 reaction:



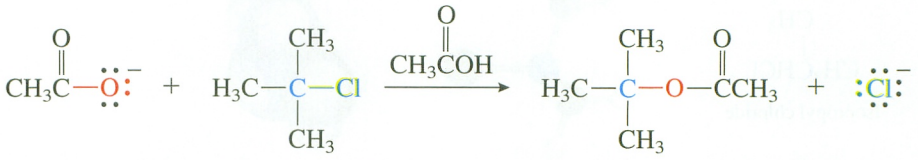
PROBLEM 8.3

Arrange these compounds in order of decreasing S_N2 reaction rate:



8.6 UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION

Now consider the reaction of acetate ion with *tert*-butyl chloride:



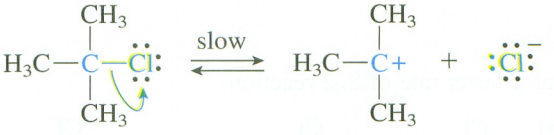
This reaction looks very similar to the reaction of hydroxide ion with methyl chloride presented earlier, but with the negative oxygen of the acetate anion acting as the nucleophile. (The CH_3CO_2H shown over the arrow is the solvent for the reaction.) However, investigation of this reaction in the laboratory has shown that the reaction rate depends only on the concentration of *tert*-butyl chloride (*t*-BuCl). It is totally independent of the concentration of acetate anion. The reaction follows the first-order rate law:

$$\text{rate} = k[t\text{-BuCl}]$$

Because the reaction follows a different rate law from the S_N2 mechanism, it must also proceed by a different mechanism.

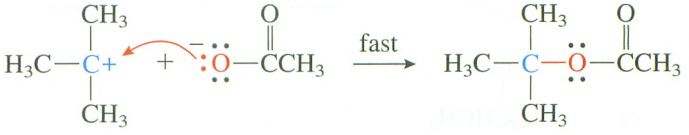
The fact that the rate law depends only on the concentration of *tert*-butyl chloride means that only *tert*-butyl chloride is present in the transition state that determines the rate of the reaction. There must be more than one step in the mechanism because the acetate ion must not be involved until after the step with this transition state. Because only one molecule (*tert*-butyl chloride) is present in the step involving the transition state that determines the rate of the reaction, this step is said to be unimolecular. The reaction is therefore described as a **unimolecular nucleophilic substitution** reaction, or an **S_N1** reaction.

The S_N1 mechanism proceeds by the following two steps:



(Step 1)

tert-Butyl carbocation
(a reactive intermediate)



(Step 2)

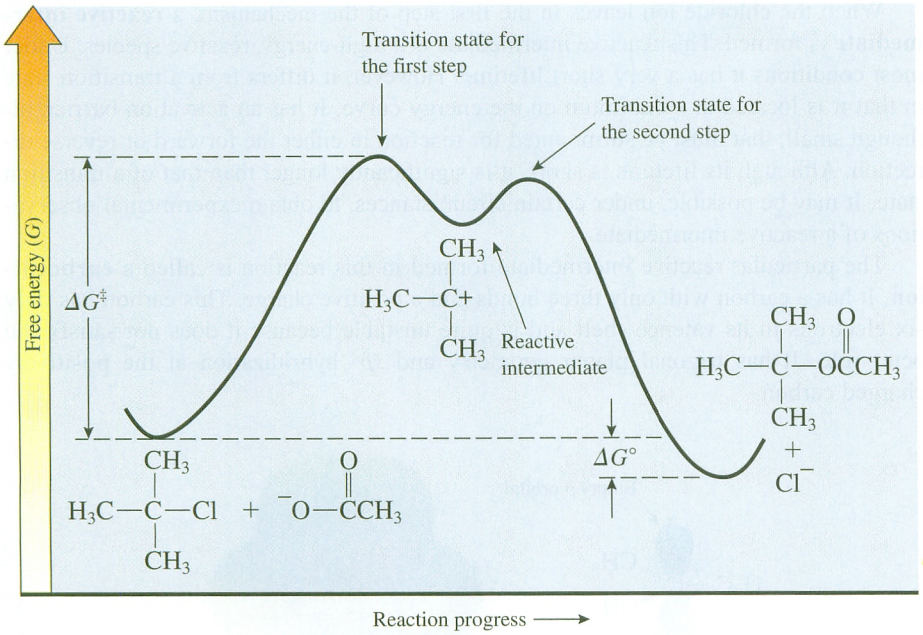


Figure 8.6

FREE ENERGY VERSUS REACTION PROGRESS DIAGRAM FOR THE S_N1 REACTION OF *TERT*-BUTYL CHLORIDE (2-CHLORO-2-METHYLPROPANE) AND ACETATE ANION.

In this mechanism, the bond to the chloride is broken in the first step and the bond to the acetate is formed in the second step. A free energy versus reaction progress diagram for the S_N1 mechanism is shown in Figure 8.6. In this reaction, each of the two steps has an energy maximum or transition state separating its reactant and product, which are both at energy minima. The transition state for the first step is at higher energy in this case. Once a molecule makes it over the higher-energy barrier of the first step, it has enough energy to proceed rapidly over the lower-energy barrier of the second step. The first step is called the **rate-limiting** or **rate-determining step** because it determines the rate of the reaction. It acts as a kind of bottleneck for the reaction. The rate of this reaction should depend only on the concentration of *tert*-butyl chloride because it is the only molecule involved in the rate-determining step. Therefore, this mechanism is consistent with the experimentally determined rate law.

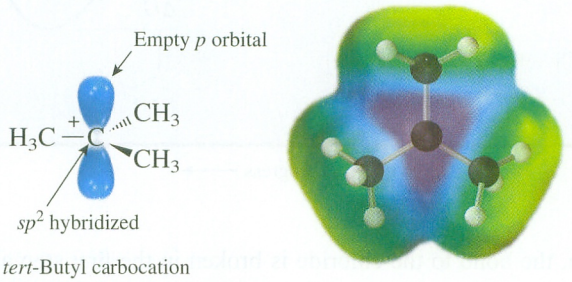
In general, for a nonconcerted reaction, that is, a reaction that proceeds in several steps, the free energy versus reaction progress diagram has a separate transition state for each step. One or more intermediates are present along the reaction pathway, each of these located at an energy minimum. These intermediates may be located at relatively high energy and have only a transient existence, such as the carbocation formed in the S_N1 reaction, or they may be located at lower energy and have a longer lifetime. If one of the transition states is located at significantly higher energy than the others, then that step is the rate-determining step for the reaction. Molecules that become involved in the mechanism after the rate-determining step do not appear in the rate law for the reaction.

PROBLEM 8.4

Draw a free energy versus reaction progress diagram for a reaction that occurs in two steps with a relatively stable intermediate and in which the transition state for the second step is the highest-energy transition state.

When the chloride ion leaves in the first step of the mechanism, a **reactive intermediate** is formed. This reactive intermediate is a high-energy, reactive species. Under most conditions it has a very short lifetime. However, it differs from a transition state in that it is located at a minimum on the energy curve. It has an activation barrier, although small, that must be surmounted for reaction in either the forward or reverse direction. Although its lifetime is short, it is significantly longer than that of a transition state. It may be possible, under certain circumstances, to obtain experimental observations of a reactive intermediate.

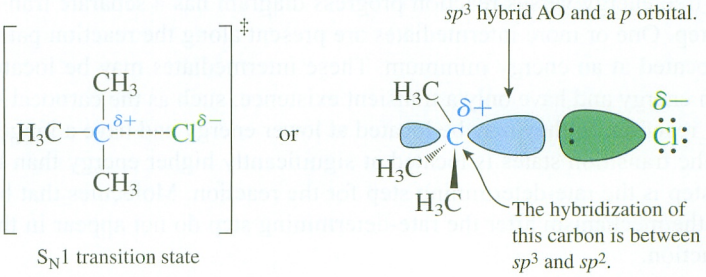
The particular reactive intermediate formed in this reaction is called a **carbocation.** It has a carbon with only three bonds and a positive charge. This carbon has only six electrons in its valence shell and is quite unstable because it does not satisfy the octet rule. It has trigonal planar geometry and sp^2 hybridization at the positively charged carbon.



tert-Butyl carbocation

Carbocations are one of the most important types of reactive intermediates in organic chemistry. They are encountered in many reactions in addition to the S_N1 reaction.

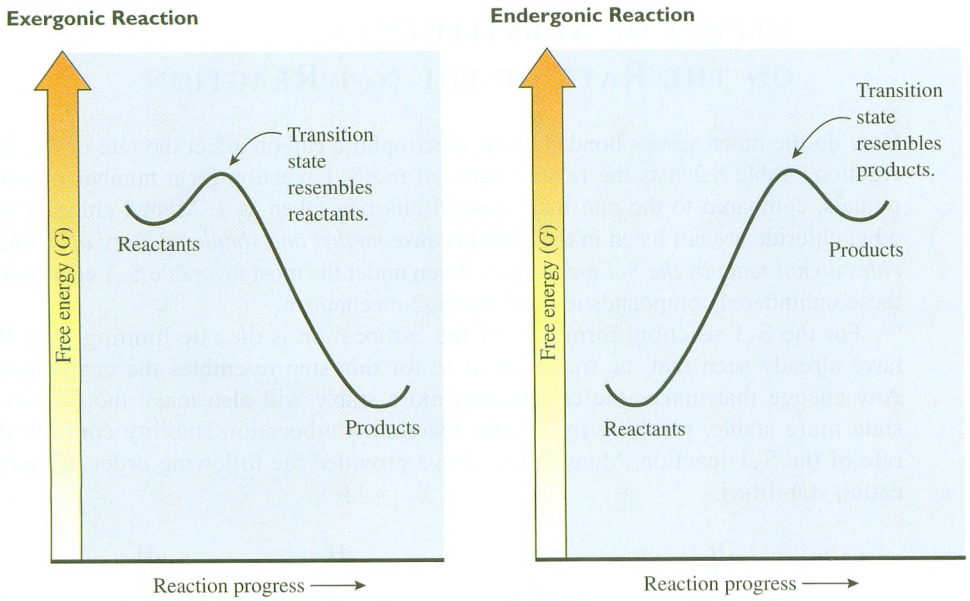
Let's now turn our attention to the transition state for this reaction. What is the structure of the transition state? This is an important question because a better understanding of its structure will help in predicting how various factors affect its stability and therefore will aid in predicting how these same factors affect the rate of the reaction. The transition state has a structure that is intermediate between that of the reactant, *tert*-butyl chloride, and that of the product, the *tert*-butyl carbocation. It has the bond between the carbon and the chlorine partially broken and can be represented as shown in the following structures:



S_N1 transition state

It has a partial positive charge on the carbon and a partial negative charge on the chlorine. The hybridization of the carbon is between that of the reactant, sp^3, and that of the carbocation, sp^2.

Is the bond in the transition state more or less than half broken? The **Hammond postulate** enables questions such as this to be answered. It states that the structure of the



a For an exergonic reaction, in which the reactants are at higher energy than the products, the energy of the transition state is closer to that of the reactants than that of the products. Therefore, the structure of the transition state resembles that of the reactants more than that of the products. If a bond is forming in the reaction, that bond is less than half formed in the transition state, and if a bond is breaking, it is less than half broken.

b For an endergonic reaction, in which the products are at higher energy than the reactants, the energy of the transition state is closer to that of the products. Therefore, its structure is also closer to that of the products. Any bonds that are forming in the reaction are more than half formed, and any bonds that are breaking are more than half broken.

Figure 8.7

USING THE HAMMOND POSTULATE TO PREDICT THE STRUCTURE OF A TRANSITION STATE **a** **EXERGONIC REACTION AND** **b** **ENDERGONIC REACTION.**

transition state for a reaction step is closer to that of the species (reactant or product of that step) to which it is closer in energy. If the product of the step is higher in energy than the reactant, the structure of the transition state is more similar to that of the product than it is to that of the reactant. In contrast, if the reactant is higher in energy than the product, the structure of the transition state is more similar to that of the reactant than the product (see Figure 8.7). Because the carbocation is much higher in energy than the starting alkyl halide (the slow step of the mechanism in Figure 8.6 corresponds to the case on the right in Figure 8.7), the structure of the transition state for the S_N1 reaction is closer to that of the carbocation; the bond is more than half broken.

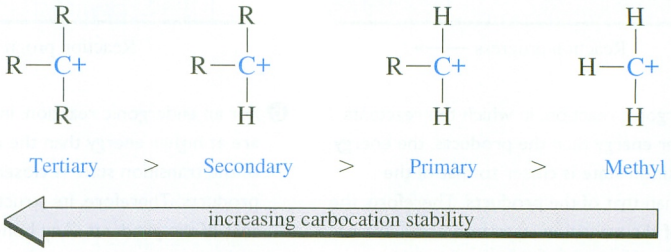
PROBLEM 8.5

Consider the free energy versus reaction progress diagram for the S_N2 reaction shown in Figure 8.1. Does the transition state for this reaction have the C—Cl bond less than half broken, approximately half broken, or more than half broken?

8.7 Effect of Substituents on the Rate of the S_N1 Reaction

How do the other groups bonded to the electrophilic carbon affect the rate of the S_N1 reaction? Table 8.2 lists the relative rates of the S_N1 reaction for a number of compounds, compared to the rate for isopropyl chloride taken as 1. Methyl chloride and ethyl chloride are not listed in the table because *methyl and simple primary alkyl chlorides do not react by the S_N1 mechanism.* Even under the most favorable S_N1 conditions, these unhindered compounds react by the S_N2 mechanism.

For the S_N1 reaction, formation of the carbocation is the rate-limiting step. We have already seen that the transition state for this step resembles the carbocation. Any change that makes the carbocation more stable will also make the transition state more stable, resulting in a faster reaction. Carbocation stability controls the rate of the S_N1 reaction. Many studies have provided the following order of carbocation stabilities:

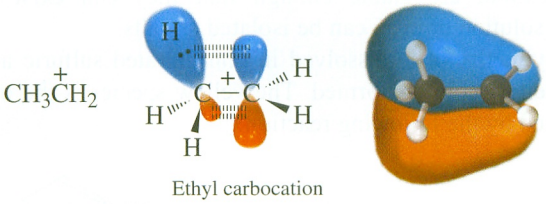


This stability order is important to remember because carbocations occur as intermediates in several other reactions.

Table 8.2 Relative Rates of S_N1 Reactions for Selected Compounds

Name	Structure	Relative Rate
Isopropyl chloride	$CH_3CH(CH_3)Cl$	1
tert-Butyl chloride	$(CH_3)_3CCl$	1×10^5
Allyl chloride	$CH_2{=}CHCH_2Cl$	3
Benzyl chloride	$PhCH_2Cl$	30
Diphenylmethyl chloride	Ph_2CHCl	1×10^4
Triphenylmethyl chloride	Ph_3CCl	1×10^9

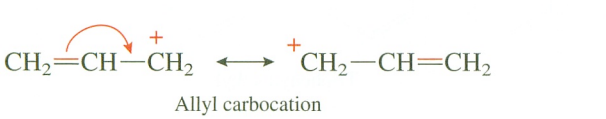
This order shows that the substitution of a methyl group for a hydrogen on a carbocation results in considerable stabilization. (The substitution of other alkyl groups provides a similar stabilization.) This is due to the overlap of a sigma bonding MO from the adjacent carbon with the empty *p* orbital of the carbocation. This overlap forms a conjugated system and allows electron density to flow from the sigma bond to the electron-deficient carbon. This overlap can be illustrated for the ethyl cation as follows:



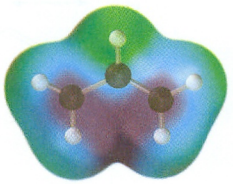
Ethyl carbocation

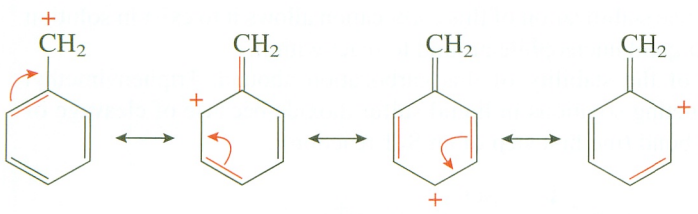
The sigma MO and the empty *p* AO are coplanar, so they overlap in a manner similar to a pi bond, even though they are not parallel. This overlap provides a path for the electrons of the sigma bond to be delocalized into the empty *p* orbital, thus helping to stabilize the carbocation. Other kinds of sigma bonds can interact with an empty *p* orbital in a similar fashion, as long as the sigma MO and the *p* AO are on adjacent carbons. Such a stabilizing interaction is termed **hyperconjugation.**

Further examination of Table 8.2 shows that allyl chloride and benzyl chloride have much faster rates for S_N1 reactions than would be expected for primary systems. Examination of the carbocations reveals that the reason for this enhanced reactivity is the significant resonance stabilization provided by the adjacent double bond or benzene ring. Resonance stabilization increases with the substitution of additional phenyl groups, as illustrated by the reaction rates of diphenylmethyl and triphenylmethyl chloride (Table 8.2).

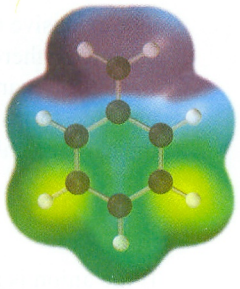


Allyl carbocation





Benzyl carbocation

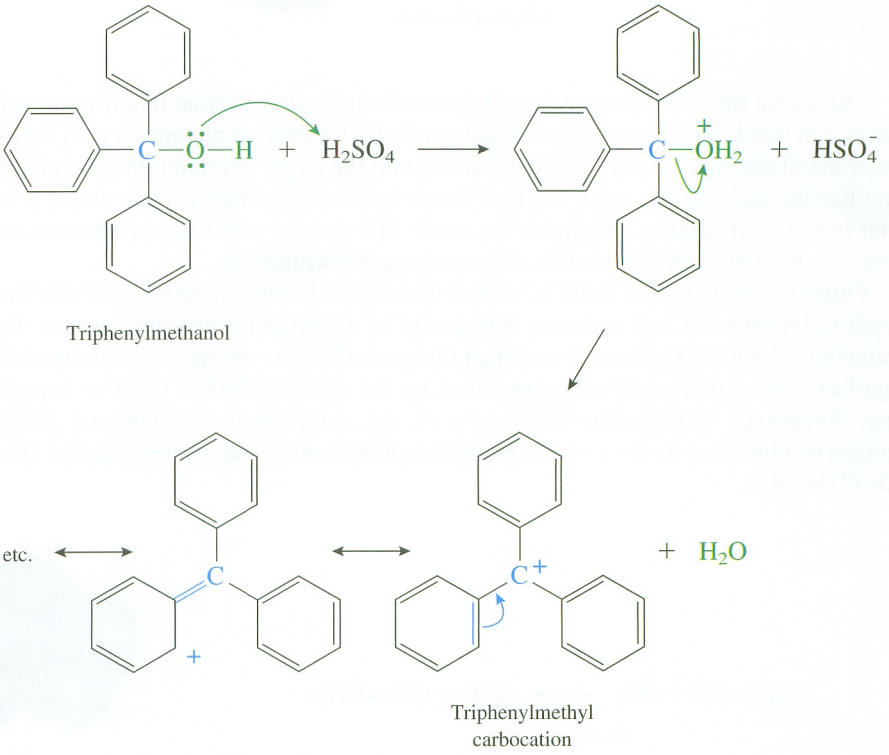


Focus On

The Triphenylmethyl Carbocation

Most carbocations are quite unstable and have only a fleeting existence as intermediates in reactions such as the S_N1 substitution. However, some, such as the triphenylmethyl carbocation, are stable enough that they can exist in significant concentrations in solution or even can be isolated as salts.

When triphenylmethanol is dissolved in concentrated sulfuric acid, a solution with an intense yellow color is formed. The yellow species is the triphenylmethyl carbocation, formed by the following reaction:

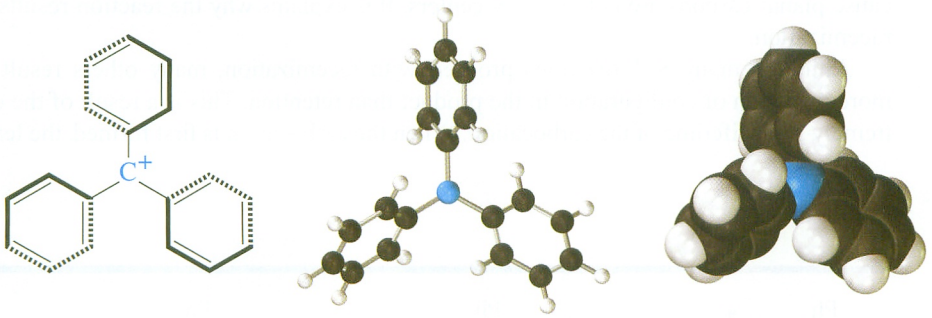


The extensive resonance stabilization of this carbocation allows it to exist in solution as long as there is no good nucleophile around to react with it.

Other examples of the stability of this carbocation abound. Triphenylmethyl chloride forms conducting solutions in liquid sulfur dioxide because of cleavage of the carbon–chlorine bond (the first step of an S_N1 reaction):

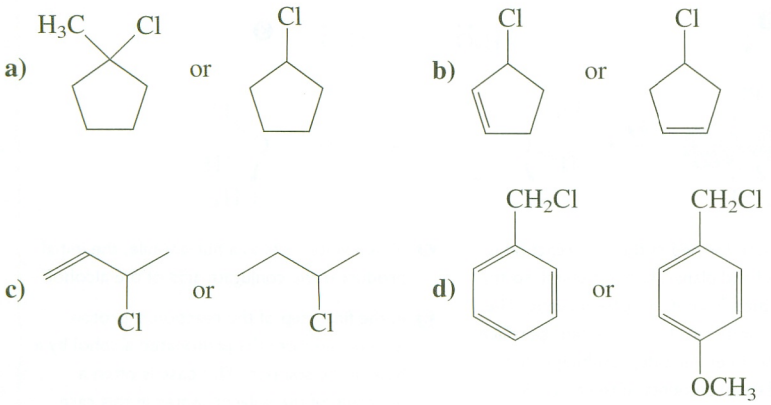
If the anion is not very nucleophilic, solid salts containing the triphenylmethyl carbocation can actually be isolated. Thus, the tetrafluoroborate salt, $Ph_3C^+\ BF_4^-$, can

be isolated and stored for years as a stable ionic solid and is even commercially available. The geometry of perchlorate salt, $Ph_3C^+ \ ClO_4^-$, has been determined by X-ray crystallography. The central carbon has planar geometry as expected for an sp^2-hybridized carbocation but the rings are twisted out of the plane because of the severe steric crowding that would occur if they were all planar, so the cation has a shape that resembles a propeller. Note that this causes a decrease in resonance stabilization (called steric hindrance to resonance) because the *p* orbitals on the benzene rings are not exactly parallel to the *p* orbital of the central carbon. Still, there is enough resonance stabilization to make this carbocation much more stable than most others.



PROBLEM 8.6

Explain which compound has a faster rate of S_N1 reaction.



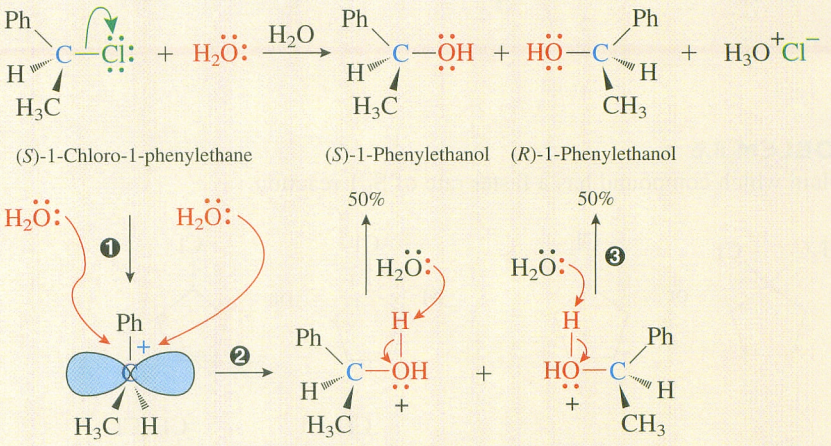
PROBLEM 8.7

Arrange these compounds in order of decreasing S_N1 reaction rate.

8.8 STEREOCHEMISTRY OF THE S_N1 REACTION

What happens in the S_N1 reaction if the leaving group is attached to a carbon that is a chirality center? A common result for the S_N1 reaction is racemization; that is, the product is formed with 50% inversion and 50% retention of configuration. An example, the reaction of (*S*)-1-chloro-1-phenylethane with water to give racemic 1-phenyl-1-ethanol, is illustrated in Figure 8.8. In this reaction the stereochemical integrity of the reactant is randomized on the pathway to the product. This usually means that there is some intermediate along the reaction pathway that is not chiral. In the case of the S_N1 reaction the carbocation intermediate is sp^2 hybridized and has trigonal planar geometry. Because planar carbons are not chirality centers, this explains why the reaction results in racemization.

Although many S_N1 reactions proceed with racemization, many others result in more inversion of configuration in the product than retention. This is a result of the extremely short lifetime of the carbocation. When the carbocation is first formed, the leav-



❶ The carbocation formed in this S_N1 reaction is sp^2 hybridized and planar. It is not chiral, so the products formed from it must be racemic. The nucleophile—water in this case—can approach equally well from either side, resulting in the formation of equal amounts of the *R* and *S* enantiomers of the product. Note that it is water, not hydroxide ion, that acts as a nucleophile because the concentration of hydroxide ion in neutral water is extremely low.

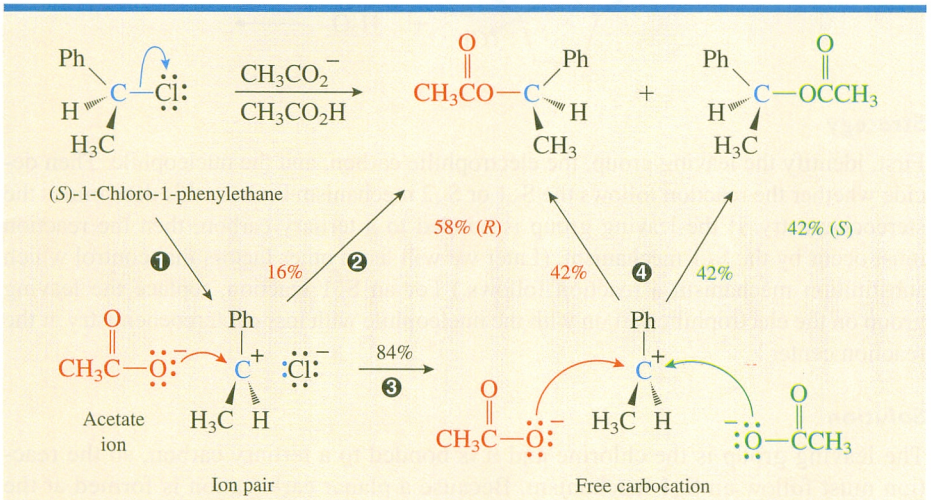
❷ When water acts as a nucleophile, the initial product is the conjugate acid of the alcohol.

❸ In the final step of the reaction, a proton is removed from the protonated alcohol by a base in the solution. This base is often a molecule of the solvent, water in this case.

Figure 8.8

MECHANISM AND STEREOCHEMISTRY OF THE S_N1 REACTION OF (*S*)-1-CHLORO-1-PHENYLETHANE IN AQUEOUS SOLUTION.

ing group is still present on the side of the carbocation where it was originally attached, as shown in Figure 8.9. This species is called an **ion pair.** If the nucleophile attacks the ion pair, the leaving group is still blocking the front side of the carbocation and inversion is favored. After the leaving group has had time to diffuse away, generating a "free" carbocation, the nucleophile can attack equally well from either side, and equal amounts of inversion and retention result. As the lifetime of the carbocation increases, it will more likely reach the free stage, resulting in more complete racemization. The lifetime of the carbocation increases as its stability increases and also depends on the nucleophile and the solvent that are used in a particular reaction. The change of nucleophile and solvent is why the reaction of 1-chloro-1-phenylethane in water (Figure 8.8) gives a different stereochemical result than the reaction of the same compound in



❶ The initial species formed in this S_N1 reaction, a carbocation with the chloride anion situated directly adjacent, is called an **ion pair.** There is a competition between reaction of the nucleophile with the ion pair and diffusion of the anion away from the carbocation.

❷ Under this particular set of reaction conditions, 16% of the ion pairs react with the nucleophile, acetate ion. Because the chloride is blocking one side of the ion pair, acetate can approach only from the opposite side. Therefore, only the product with inverted configuration is formed when the nucleophile reacts at this stage.

❸ For the other 84% of the ion pairs, the chloride ion diffuses away before the nucleophile attacks.

❹ The nucleophile can approach the resulting free carbocation equally well from either side, resulting in the formation of equal amounts of product with retained and inverted configuration (42% of each). The final result is 42% retention and 16% + 42% = 58% inversion. The reaction has occurred with racemization and some excess inversion.

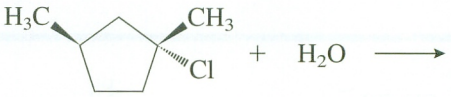
Figure 8.9

STEREOCHEMISTRY OF THE S_N1 REACTION OF (*S*)-1-CHLORO-1-PHENYLETHANE IN ACETIC ACID CONTAINING POTASSIUM ACETATE.

acetic acid containing potassium acetate (Figure 8.9). The carbocation has a longer lifetime under the reaction conditions of Figure 8.8 than under those of Figure 8.9 (see problem 8.14), allowing the chloride ion time to diffuse away before the nucleophile attacks, resulting in the formation of a racemic product. The shorter-lived carbocation of Figure 8.9 reacts partly at the ion-pair stage, resulting in more inversion than retention. In summary, S_N1 reactions occur with racemization, often accompanied by some excess inversion. We will not attempt to predict the exact amount of each enantiomer that is produced.

PRACTICE PROBLEM 8.1

Show the product, including stereochemistry, of this reaction:

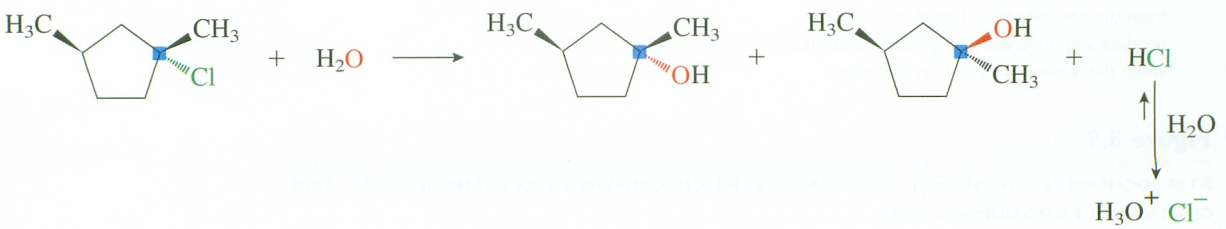


Strategy

First, identify the leaving group, the electrophilic carbon, and the nucleophile. Then decide whether the reaction follows the S_N1 or S_N2 mechanism because this determines the stereochemistry. If the leaving group is bonded to a tertiary carbon, then the reaction must occur by the S_N1 mechanism. (Later we will learn other factors that control which substitution mechanism a reaction follows.) For an S_N1 reaction, replace the leaving group on the electrophilic carbon with the nucleophile with loss of stereochemistry at the reaction center.

Solution

The leaving group is the chlorine and it is bonded to a tertiary carbon, so the reaction must follow an S_N1 mechanism. Because a planar carbocation is formed at the reaction center, the nucleophile, H_2O, can bond to either side of the cyclopentane ring. Stereochemistry is lost at the electrophilic carbon, but there is no change at the other chirality center because the reaction does not involve that carbon. Because the two products, one with the methyl groups cis and the other with the methyl groups trans, are diastereomers, they, along with the transition states leading to them, may have different energies. Therefore, the two alcohol products are not necessarily formed in equal amounts even if all of the carbocation makes it to the "free" stage. However, the stabilities of the products are not very different so similar amounts of both are expected.



PROBLEM 8.8

Show the products, including stereochemistry, of these S_N1 reactions:

a) $CH_3CH_2C(Ph)(CH_3)Cl + CH_3OH \longrightarrow$

b) $CH_3CH_2C(H)(CH_3C(CH_3)_2Cl)CH_2 + CH_3COH \longrightarrow$

8.9 Leaving Groups

The bond to the leaving group is broken during the rate-determining step in both the S_N1 and S_N2 reactions. Therefore, the structure of the leaving group affects the rates of both of these reactions. Although the only leaving group we have seen so far is chloride, there are others that can be used. In general, the more stable the leaving group is as a free species—that is, after it has left—the faster it will leave. This stability is also reflected in the basicity of the species: the more stable it is, the weaker base it is. In general, the leaving groups that are used in the S_N1 and the S_N2 reactions are weak bases. Table 8.3 lists the most important leaving groups and provides their relative reaction rates in an S_N1 reaction. Similar rate effects are found for S_N2 reactions.

As can be seen from Table 8.3, the leaving ability of the halides increases as one goes down the column of the periodic table; that is, Cl^- is the slowest, Br^- is faster, and

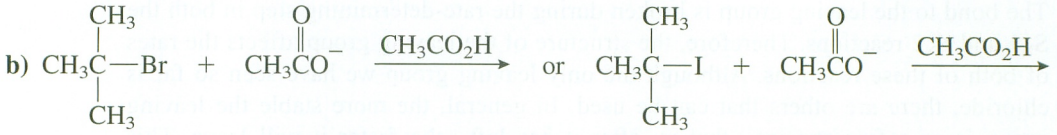
Table 8.3 Approximate Reactivities of Some Important Leaving Groups

Structure	Leaving Group	Name	Relative Reactivity
R—Cl	Cl^-	Chloride	1
R—Br	Br^-	Bromide	10
$R-\overset{+}{O}H_2$	OH_2	Water	10
R—I	I^-	Iodide	10^2
$R-O-S(=O)(=O)-CH_3$	$^-O-S(=O)(=O)-CH_3$	Mesylate (methanesulfonate)	10^4
$R-O-S(=O)(=O)-C_6H_4-CH_3$	$^-O-S(=O)(=O)-C_6H_4-CH_3$	Tosylate (*p*-toluenesulfonate)	10^4

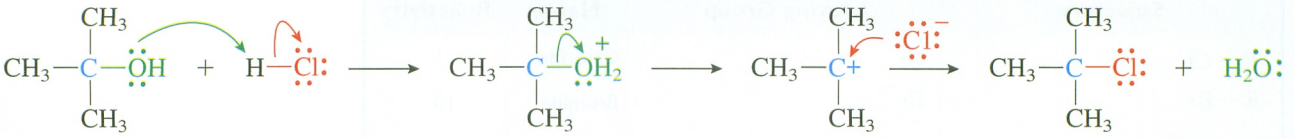
I^- is the fastest. This order parallels the decrease in basicity that occurs as one proceeds down a column of the periodic table. Fluoride ion (F^-) is so slow that it is not commonly used as a leaving group.

PROBLEM 8.9

Explain whether these reactions would follow the S_N1 or the S_N2 mechanism and then explain which reaction is faster:

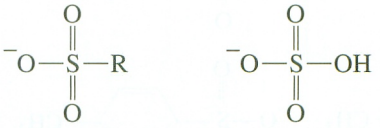


Because alcohols are very common and easily prepared by a variety of methods, it would be useful to be able to use OH as a leaving group in nucleophilic substitution reactions. However, OH^- is much too basic to act as a leaving group in S_N1 and S_N2 reactions. It is necessary to modify the OH, converting it to a better leaving group, to use alcohols as substrates for these reactions. Several methods have been developed to accomplish this goal. If the reaction of the alcohol is conducted in acidic solution, the oxygen becomes protonated, producing ROH_2^+. The leaving group is now water, which is comparable to bromide in reactivity. (Of course, to use this leaving group, the nucleophile must be stable in acidic solution.) An example is provided in the following equation:



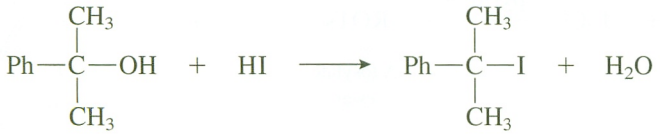
ORGANIC Chemistry Now™
Click *Mechanisms in Motion* to view this **S_N1 Mechanism.**

Another method that can be used to transform the hydroxy group of an alcohol into a leaving group is to replace the hydrogen with some other group that significantly decreases the basicity of the oxygen. A group that is commonly used for this purpose is the SO_2R group. Replacing the hydrogen of the alcohol with this group produces a sulfonate ester, such as the mesylate or tosylate ester shown in Table 8.3. As can be seen by their resemblance to the bisulfate anion (the conjugate base of sulfuric acid), sulfonate anions are weak bases and excellent leaving groups.



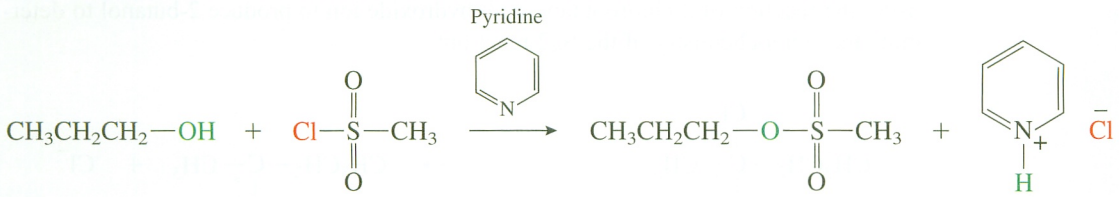
PROBLEM 8.10

a) Show all the steps in the mechanism for this reaction. Don't forget to use curved arrows to show the movement of electrons in each step of the mechanism.



b) Show a free energy versus reaction progress diagram for the reaction of part a.

Primary and secondary alcohols are readily converted to mesylate or tosylate esters by reaction with the corresponding sulfonyl chloride. The mesylate and tosylate esters derived from tertiary alcohols are too reactive and cannot be isolated. (Although we will not go into the mechanism of these reactions in detail at this point, the reactions involve the attack of the oxygen [the nucleophile] of the alcohol at the sulfur [the electrophile], ultimately displacing chloride [the leaving group].) Pyridine is often used as a solvent for these preparations in order to react with the HCl that is produced as a by-product. An example of the preparation of a methanesulfonate (mesylate) ester is shown in the following equation:

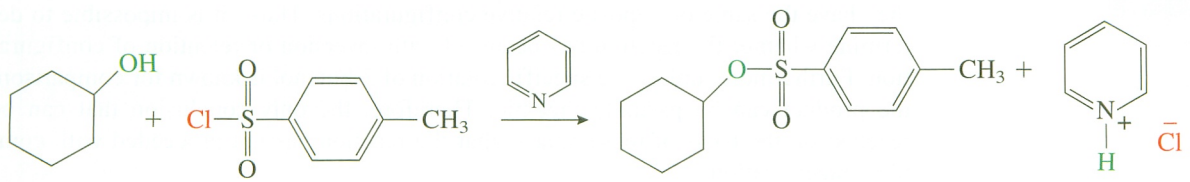


1-Propanol — Methanesulfonyl chloride — Propyl mesylate

or, in more general form:

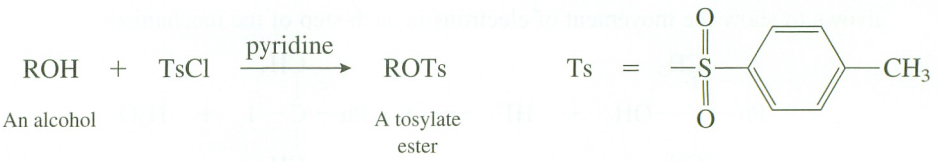
An alcohol — A mesylate ester

An example of the preparation of a tosylate ester is shown in the following equation:



Cyclohexanol — *p*-Toluenesulfonyl chloride — Cyclohexyl tosylate

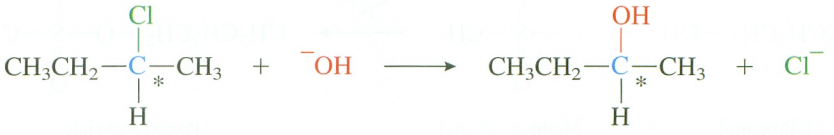
or, in more general form:



In summary, the halide ions, Cl^-, Br^-, and I^-, are common leaving groups for these nucleophilic substitution reactions. The OH of an alcohol can be converted to a leaving group by protonation in acid solution or by conversion to a mesylate or tosylate ester. The OR^- of an ether, like the OH^- of an alcohol, is too basic to leave. Likewise, NH_2^- (from an amine), H^- (from breaking C—H bonds of alkanes), and R_3C^- (carbanions from breaking C—C bonds of alkanes) are much too basic and *do not act as leaving groups in these reactions*.

The tosylate leaving group was used in one of the classic experiments that was used to determine the stereochemistry of the S_N2 reaction. Now that we know about this leaving group, let's look at the experiment and see how it helped establish that S_N2 reactions occur with inversion of configuration.

Designing an experiment to demonstrate that an S_N2 reaction occurs with inversion of configuration is not as simple as it might appear at first glance. For example, consider using the reaction of 2-chlorobutane with hydroxide ion to produce 2-butanol to determine the stereochemistry of the S_N2 reaction:

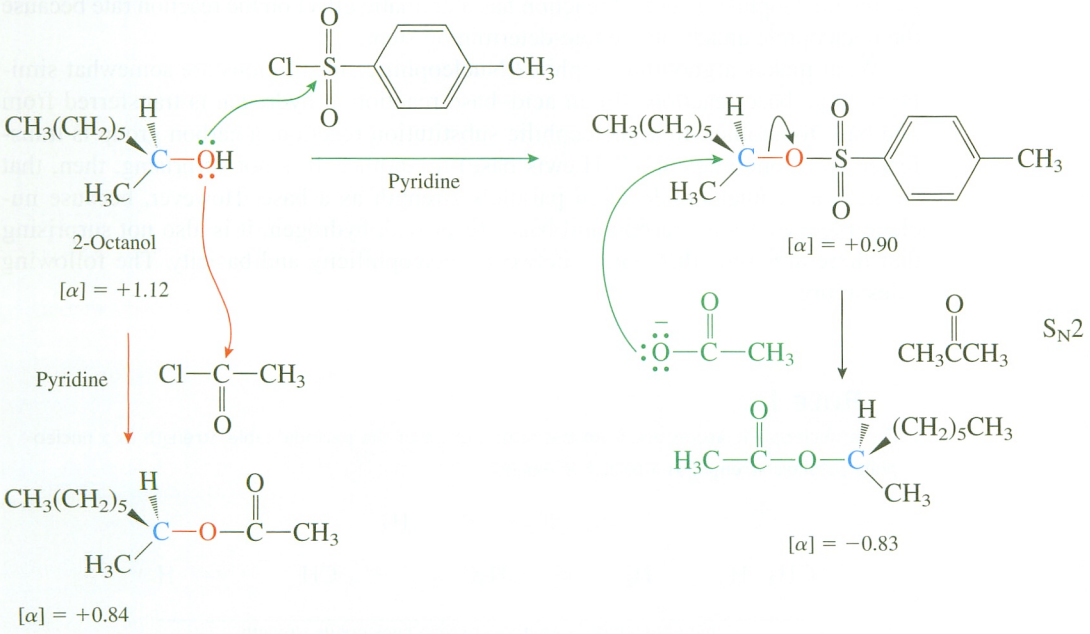


2-Chlorobutane 2-Butanol

First, it must be established that this reaction proceeds by an S_N2 mechanism. To do this, the experimental rate law for the reaction is determined. Because the reaction is found to follow the second-order rate law, rate = k[2-chlorobutane][hydroxide ion], it is proceeding by the S_N2 mechanism. Then the stereochemistry of the product is investigated. Suppose that the starting 2-chlorobutane has $[\alpha] = +8.5$ and the 2-butanol formed in the reaction has $[\alpha] = -13.9$. What can be deduced from this information? Remember, there is no relationship between the sign of the rotation and the configuration of a compound. So, even though the starting 2-chlorobutane and the product 2-butanol have opposite signs for their rotations, we do not know whether they have the same or opposite relative configurations. Thus, it is impossible to determine whether the reaction has occurred with inversion or retention of configuration. Furthermore, unless the specific rotation of 2-butanol is known for comparison, the product can be partially racemic. Therefore, the only conclusion that can be reached on the basis of these data is that the reaction has not proceeded with complete racemization.

To determine the stereochemistry of the reaction, a method must be found to relate the configuration of the reactant to that of the product. The following experiment shows

one method that has been used to accomplish this. A sample of 2-octanol with $[\alpha] = +1.12$ was converted to its tosylate ester, which had $[\alpha] = +0.90$. In this reaction the O of the alcohol displaces the Cl of *p*-toluenesulfonyl chloride. Because the carbon–oxygen bond of the alcohol is not broken in this reaction, the tosylate ester must have the same relative configuration as the alcohol.



The S_N2 reaction of the tosylate ester with acetate ion in acetone as solvent produced an ester with $[\alpha] = -0.83$. (Again, the configuration of the product cannot be determined solely on the basis of this experiment.)

To determine its stereochemistry, the ester was prepared by an alternate pathway. Reaction of the starting alcohol with acetyl chloride (CH_3COCl) produced the ester with $[\alpha] = +0.84$. This reaction, like the formation of the tosylate ester, does not involve breaking the carbon–oxygen bond of the alcohol, so the ester obtained in this reaction must have the same relative configuration as both the alcohol and the *p*-toluenesulfonate ester. Comparison of the rotation of this ester, ($[\alpha] = +0.84$) with that of the ester obtained as the product of the S_N2 reaction ($[\alpha] = -0.83$) demonstrated that they have opposite relative configurations. Therefore, the S_N2 reaction has occurred with complete inversion of configuration, within experimental error. It is interesting to note that it not necessary to know the absolute configuration of any of the compounds in this reaction cycle to determine that the S_N2 reaction has proceeded with inversion of configuration. Nor is it necessary that the original alcohol be enantiomerically pure—that is, that it be composed of a single enantiomer. In fact, in the experiment described here, the enantiomeric purity of the original 2-octanol was only 11%.

A large number of other experiments have been performed, and in each case the results have been the same. S_N2 reactions have always been found to proceed with complete inversion of configuration.

8.10 NUCLEOPHILES

In the case of an S_N1 reaction, the nucleophile does not become involved until after the rate-determining step. Therefore, changing the nucleophile has no effect on the *rate* of an S_N1 reaction, although it may change the *product* of the reaction. In contrast, changing the nucleophile in an S_N2 reaction has a dramatic effect on the reaction rate because the nucleophile attacks in the rate-determining step.

What makes a good nucleophile? Nucleophilic substitutions are somewhat similar to acid–base reactions. In an acid–base reaction, a hydrogen is transferred from one base to another. In a nucleophilic substitution reaction, a carbon group is transferred from one nucleophile (Lewis base) to another. It is not surprising, then, that strength as a nucleophile often parallels strength as a base. However, because nucleophiles react with carbon and bases react with hydrogen, it is also not surprising that there are some differences between nucleophilicity and basicity. The following rules apply.

▶ RULE 1

If the nucleophilic atoms are from the same period of the periodic table, strength as a nucleophile parallels strength as a base. For example,

$$H_2O < NH_3$$

$$CH_3OH \approx H_2O < CH_3CO_2^- < CH_3O^- \approx HO^-$$

increasing base strength/increasing nucleophile strength

▶ RULE 2

Nucleophile strength increases down a column of the periodic table (in solvents that can hydrogen bond, such as water and alcohols). For example,

$$RO^- < RS^-$$

$$R_3N < R_3P$$

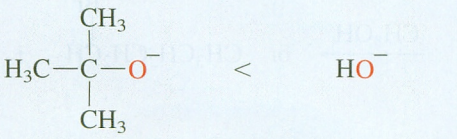
$$F^- < Cl^- < Br^- < I^-$$

increasing nucleophile strength/decreasing base strength

In these cases the change in nucleophile strength is opposite to the change in base strength. This is due at least in part to the stronger hydrogen bonding that occurs between the smaller ions and solvent molecules of water or alcohols. The resulting tighter arrangement of solvent molecules around the nucleophile makes it more difficult for the electrophilic carbon to approach.

RULE 3

Steric bulk decreases nucleophilicity. For example,



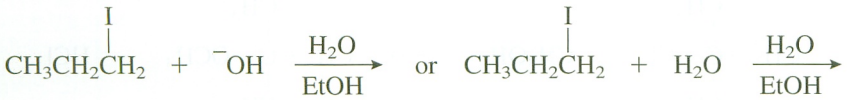
tert-Butoxide ion
Weaker nucleophile, stronger base

Stronger nucleophile
Weaker base

Because the presence of bulky groups at the electrophilic carbon slows the rate of S_N2 reactions, it is reasonable that the presence of bulky groups on the nucleophile will also slow the reaction. The steric bulk of the *tert*-butoxide ion causes it to be a much weaker nucleophile than hydroxide ion even though it is a stronger base. Therefore, *tert*-butoxide ion is often used when a strong base that is not very nucleophilic is needed.

PRACTICE PROBLEM 8.2

Explain which reaction proceeds at a faster rate:



Strategy

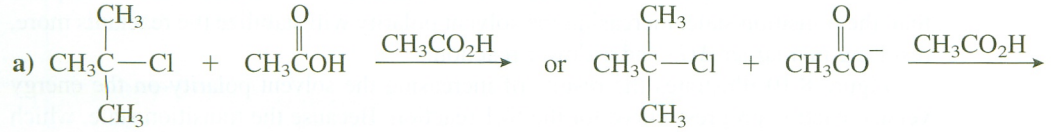
First identify the leaving group, the electrophilic carbon, and the nucleophile. If the leaving group is on a primary carbon, then the mechanism that the reaction follows is S_N2. If the leaving group is on a tertiary carbon, then the mechanism is S_N1. (We will learn how to determine the mechanism if the leaving group is on a secondary carbon in Section 8.12.) Then identify the difference between the two reactions and analyze how this difference will affect the rate.

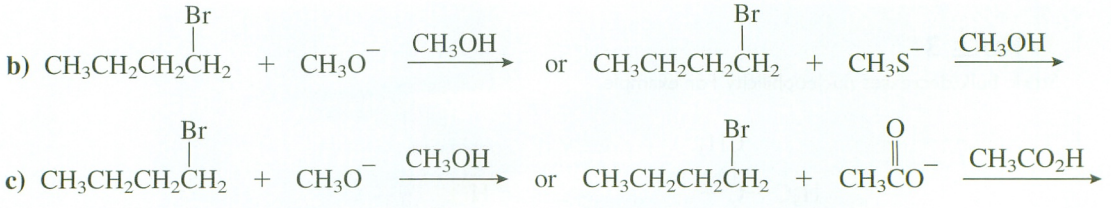
Solution

Because the leaving group is on a primary carbon, the reaction proceeds by an S_N2 mechanism. The left reaction will be faster because hydroxide ion is a stronger base and, thus, a better nucleophile than water.

PROBLEM 8.11

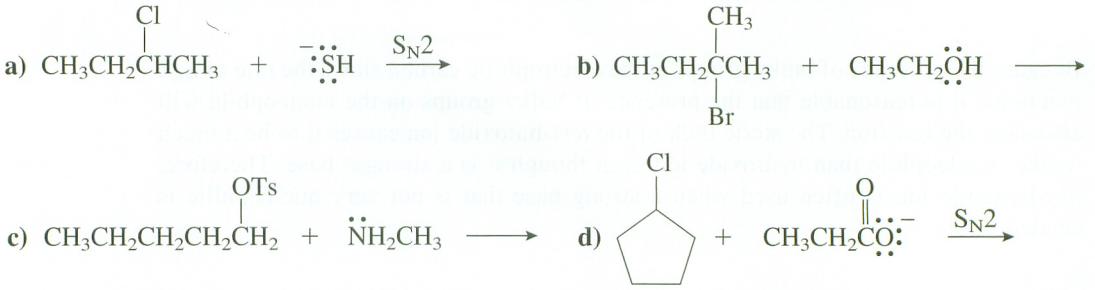
Explain which of these reactions proceeds at a faster rate:




b) CH3CH2CH2CH2Br + CH3O− CH3OH
or CH3CH2CH2CH2Br + CH3S− CH3OH
c) CH3CH2CH2CH2Br + CH3O− CH3OH
or CH3CH2CH2CH2Br + CH3CO− CH3CO2H

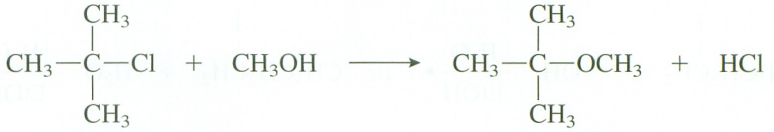
PROBLEM 8.12

Show the products and the mechanisms of the following reactions. Don't forget to use curved arrows to show the movement of electrons in each step of the mechanism.



PROBLEM 8.13

Show all of the steps in the mechanism for this reaction:



8.11 Effect of Solvent

The solvent has several roles to play in an organic reaction. It must dissolve the reagents so that they can come in contact with one another. It must not react with or decompose any of the reagents. In addition, for reactions that involve ionic or polar molecules (as reactants, intermediates, or products), the polarity of the solvent often dramatically affects the reaction rate.

Polar solvents help to stabilize ions and polar molecules. To understand the effect of the solvent polarity on reaction rates, the polarity of the reactant must be compared with the polarity of the transition state. The one (reactant or transition state) that is more polar (has more charge separation) will be stabilized more by an increase in the polarity of the solvent. If the transition state is more polar than the reactants, increasing the solvent polarity will stabilize the transition state more than the reactants. This will decrease $\Delta G^{\ddagger}$, resulting in a faster reaction. In contrast, if the reactants are more polar than the transition state, increasing the solvent polarity will stabilize the reactants more, resulting in a larger $\Delta G^{\ddagger}$ and a slower reaction.

Figure 8.10 illustrates the results of increasing the solvent polarity on the energy versus reaction progress curve for the S_N1 reaction. Because the transition state, which resembles the carbocation, is more polar than the reactant, the rate of an S_N1 reaction is much faster in a more polar solvent.

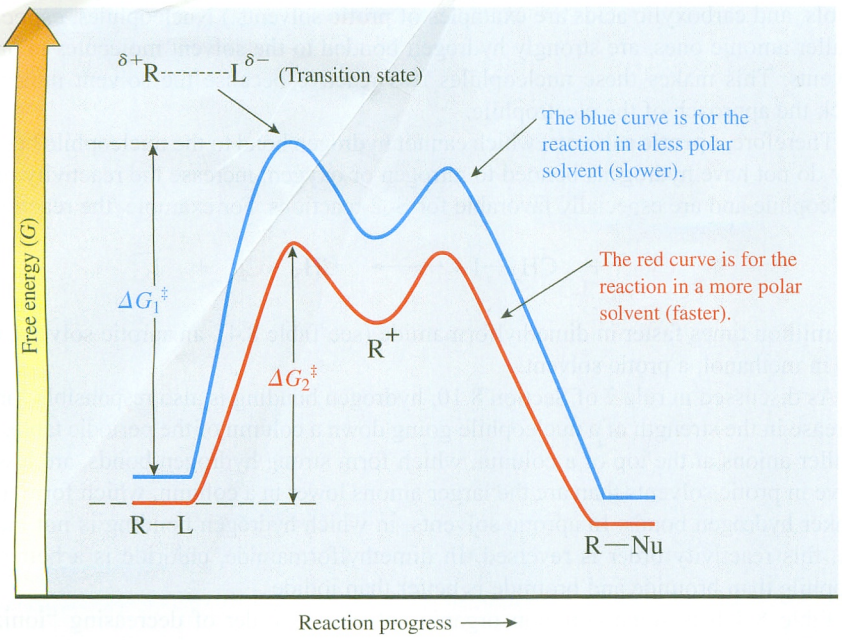
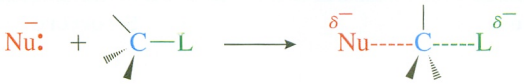

δ+ R---------L δ− (Transition state)
The blue curve is for the reaction in a less polar solvent (slower).
The red curve is for the reaction in a more polar solvent (faster).
Free energy (G)
ΔG1‡
ΔG2‡
R+
R—L
R—Nu
Reaction progress

Figure 8.10

EFFECT OF CHANGING SOLVENT POLARITY ON THE S_N1 REACTION. Because the transition state is more polar (has more charge separation) than the reactant, the change to a more polar solvent stabilizes the transition state more than it stabilizes the reactant. This results in $\Delta G_1^{\ddagger}$, the activation energy in the less polar solvent, being larger than $\Delta G_2^{\ddagger}$, the activation energy in the more polar solvent. Therefore, the reaction is faster in the more polar solvent. This diagram applies for all S_N1 reactions.

The effect of the solvent polarity on the rate of the S_N2 reaction depends on the charge that is initially present on the nucleophile. If the nucleophile has a negative charge, the reaction can be represented as



Reactants (more polar) — Transition state (less polar)

Although both the reactants and the transition state have a total charge of −1, this charge is more dispersed in the transition state. Increasing the solvent polarity stabilizes the concentrated charge of the reactant nucleophile more than the transition state, resulting in a slower reaction rate. Therefore, the rate of an S_N2 reaction involving a negative nucleophile is slower in a more polar solvent.

If the nucleophile in an S_N2 reaction is neutral, the reaction can be represented as

Reactants (less polar) — Transition state (more polar)

The reactants are neutral, whereas charges have partially formed in the transition state. In this situation the transition state is stabilized more than the reactants as the solvent is changed to a more polar one. Therefore, the rate of an S_N2 reaction involving a neutral nucleophile is faster in a more polar solvent.

In addition to these polarity effects, the ability of certain solvents to form hydrogen bonds to the nucleophile also affects the rate of the S_N2 reaction. Such solvents are termed **protic solvents** and have a hydrogen bonded to nitrogen or oxygen. (Water, al-

cohols, and carboxylic acids are examples of protic solvents.) Nucleophiles, especially smaller anionic ones, are strongly hydrogen bonded to the solvent molecules in protic solvents. This makes these nucleophiles less reactive because the solvent molecules block the approach of the electrophile.

Therefore, **aprotic solvents,** which cannot hydrogen bond to the nucleophile because they do not have hydrogens bonded to nitrogen or oxygen, increase the reactivity of the nucleophile and are especially favorable for S_N2 reactions. For example, the reaction

$$Cl^- + CH_3{-}I \longrightarrow CH_3{-}Cl + I^-$$

is 1 million times faster in dimethylformamide (see Table 8.4), an aprotic solvent, than it is in methanol, a protic solvent.

As discussed in rule 2 of Section 8.10, hydrogen bonding is also responsible for the increase in the strength of a nucleophile going down a column of the periodic table. The smaller anions at the top of a column, which form strong hydrogen bonds, are less reactive in protic solvents than are the larger anions lower in a column, which form much weaker hydrogen bonds. In aprotic solvents, in which hydrogen bonding is not important, this reactivity order is reversed. In dimethylformamide, chloride is a better nucleophile than bromide and bromide is better than iodide.

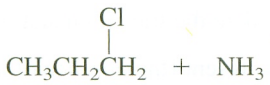
Table 8.4 lists some common organic solvents in order of decreasing "ionizing power" (or ability to stabilize ions).

Table 8.4 Some Common Solvents for Substitution Reactions

	Name	Structure	
increasing ionizing power ↑	Trifluoroacetic acid	CF_3COH	These are polar, protic solvents. They are quite good at stabilizing ions and are especially favorable for S_N1 reactions, although they can also be used for S_N2 reactions with favorable substrates.
	Water	H_2O	
	Methanol	CH_3OH	
	Acetic acid	CH_3COH	
	Ethanol	CH_3CH_2OH	
	Dimethylsulfoxide (DMSO)	CH_3SCH_3	These aprotic solvents are still relatively polar, so they can dissolve both the nucleophile and the substrate. They are especially favorable for S_N2 reactions because nucleophiles are more reactive in these solvents than in protic ones.
	Dimethylformamide (DMF)	$HCN(CH_3)_2$	
	Acetone	CH_3CCH_3	

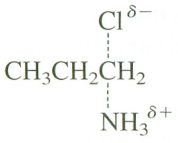
PRACTICE PROBLEM 8.3

Explain whether the reaction of 1-chloropropane with ammonia would be faster in 20% CH_3OH/80% H_2O or in 40% CH_3OH/60% H_2O as the solvent.



Solution

This is an S_N2 reaction with a neutral nucleophile.



Transition state

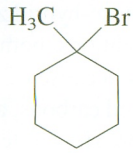
The transition state for the reaction is more polar than the reactants so the reaction is faster in a more polar solvent. Water is more polar than methanol, so the reaction is faster in 20% CH_3OH/80% H_2O than in 40% CH_3OH/60% H_2O.

PROBLEM 8.14

Explain why the carbocation shown in Figure 8.8 has a longer lifetime than it does under the conditions shown in Figure 8.9.

PROBLEM 8.15

Explain in which solvent these reactions are faster:

a)  in CH_3OH or CH_3CH_2OH

b) $CH_3CH_2CH_2\underset{\displaystyle I}{\underset{|}{C}}H_2 + {}^{-}OH$ in CH_3OH or 50% CH_3OH / 50% H_2O

c) $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}H_2 + :\bar{C}{\equiv}N:$ in CH_3CH_2OH or DMSO

8.12 COMPETITION BETWEEN S_N1 AND S_N2 REACTIONS

It is possible to examine a particular reaction and determine whether it is expected to proceed by an S_N1 or an S_N2 mechanism.

The S_N1 pathway is favored in the following circumstances:

1. The carbocation is stabilized (tertiary or resonance stabilized carbocations are best; secondary carbocations are acceptable if other factors are favorable; primary carbocations are not formed).
2. The solvent is polar (to stabilize the transition state).
3. Only poor nucleophiles are present (the absence of a good nucleophile slows the rate of a competing S_N2 reaction).

The S_N2 pathway is favored in the following circumstances:

1. The electrophilic carbon is not sterically hindered (reactions at methyl and primary carbons are excellent; reactions at secondary carbons are acceptable; S_N2 reactions do not occur at tertiary carbons).
2. Strong nucleophiles are present.
3. The solvent is aprotic (to make the nucleophile more reactive).

On the basis of these principles, Table 8.5 lists the preferred mechanism followed by different types of electrophilic carbon groups. Compounds with the leaving group on a methyl or a primary carbon react by the S_N2 mechanism. Compounds with the leaving group on a secondary, an allylic, or a benzylic carbon can react by either mechanism, depending on the solvent and the nucleophile. And compounds with the leaving group on a tertiary carbon react by the S_N1 mechanism. Compounds with the leaving group on a neopentyl type carbon do not react by an S_N1 mechanism (because the carbocation formed is primary) and also react very slowly by an S_N2 mechanism (because of the large amount of steric hindrance provided by the *tert*-butyl group). However, acceptable yields in S_N2 reactions can be obtained if an aprotic solvent is used.

The last two examples in Table 8.5 have the leaving group bonded to an sp^2-hybridized carbon, either a vinylic carbon or an aromatic carbon. Under normal conditions, both of these types of compounds are inert to nucleophilic substitution reactions because of the stronger C—L bond, the difficulty in forming carbocations at sp^2-hybridized carbons, and the extra steric hindrance to approach of the nucleophile from the side opposite the leaving group. (Under particularly favorable circumstances, S_N1 reactions of these compounds can be forced to occur.)

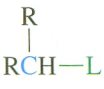
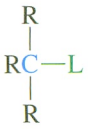
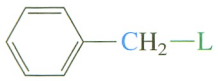
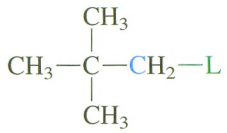
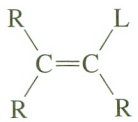
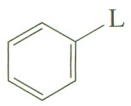
PRACTICE PROBLEM 8.4

Explain whether these reactions follow an S_N1 or an S_N2 mechanism:

a) $CH_3CH_2CH_2\underset{\displaystyle OTs}{\underset{|}{C}}H_2 + Cl^- \xrightarrow{CH_3OH}$

b) $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 + H_2O \xrightarrow[EtOH]{H_2O}$

Table 8.5 Preferred Substitution Mechanisms for Various Carbon Substrates

Type	Representative Structure	Preferred Mechanism
Methyl	$CH_3—L$	S_N2
Primary	$RCH_2—L$	S_N2
Secondary		S_N2 (with good nucleophiles; solvent can be protic or, better, aprotic) or S_N1 (with poor nucleophiles and polar solvents)
Tertiary		S_N1
Allylic	$CH_2=CHCH_2—L$	S_N2 (with good nucleophiles; solvent can be protic or, better, aprotic) or S_N1 (with poor nucleophiles and polar solvents)
Benzylic		
Neopentyl		Very slow S_N1 and S_N2 (S_N2 in aprotic solvents gives acceptable yields)
Vinylic		Inert to both S_N1 and S_N2 under normal reaction conditions
Aromatic		

Strategy

Identify the leaving group, the electrophilic carbon (the one bonded to the leaving group), the nucleophile, and the solvent (usually over the arrow). If the electrophilic carbon is methyl or a simple primary carbon, the mechanism is S_N2. If the electrophilic carbon is tertiary, the mechanism is S_N1. If the electrophilic carbon is secondary, allylic, or benzylic, you must examine the nucleophile and the solvent. With good nucleophiles, the mechanism is S_N2. (Aprotic solvents make the nucleophile even stronger.) With poor nucleophiles and polar solvents, the mechanism is S_N1.

Solution

a) The leaving group (OTs) is on a primary carbon, so the reaction follows an S_N2 mechanism. It does not matter what the nucleophile or solvent is.

b) The leaving group (Cl) is on a secondary carbon, so the mechanism depends on the nucleophile and the solvent. Water is both the nucleophile and one component of the solvent. Because water is not a strong nucleophile and the solvent (H_2O/CH_3CH_2OH) is polar, the reaction follows an S_N1 mechanism.

PROBLEM 8.16

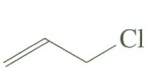
Explain whether these reactions follow an S_N1 or an S_N2 mechanism.

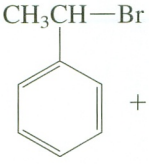
a) $CH_3C(CH_3)_2Br + CH_3CO^-$ (CH_3CO_2H)

b) + ^-SH (DMF)

c) $CH_3I + CH_3C(CH_3)_2O^-$ (*t*-BuOH)

d) + CH_3OH (CH_3OH)

e)  + CH_3CO^- (CH_3CCH_3, O)

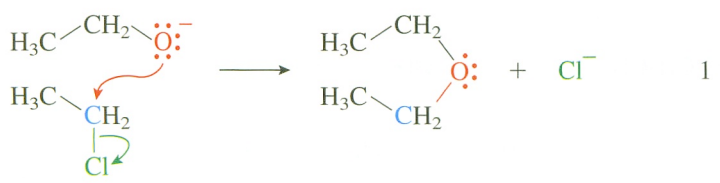
f)  + CH_3CH_2OH (EtOH)

8.13 INTRAMOLECULAR REACTIONS

The reactions discussed so far have been **intermolecular reactions;** that is, they involve two separate molecules: the nucleophile and the compound with the leaving group. It is also possible for the nucleophile and the leaving group to be part of the same molecule. In such a case the reaction is **intramolecular**—that is, within the same mol-

ecule. Examples of an intermolecular nucleophilic substitution reaction and a comparable intramolecular reaction are as follows:

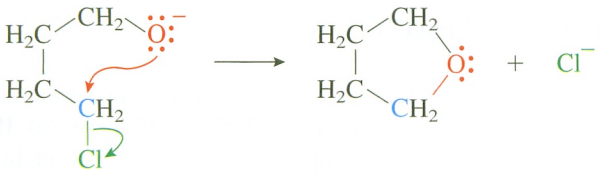
Intermolecular reaction



Relative rate

1

Intramolecular reaction



Relative rate

5000

Because the nucleophile and the electrophilic carbon are attached by a series of atoms, intramolecular reactions result in the formation of rings. If the ring formed is three, five, or six membered, the intramolecular reaction is much more favorable than its intermolecular counterpart. For example, the preceding intramolecular reaction occurs more than 5000 times faster than its intermolecular counterpart.

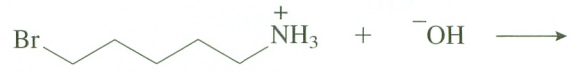
Intramolecular reactions are favored by entropy. Recall that entropy is a measure of the disorder of a system. It costs energy to put order into a system—to decrease the entropy of that system. In the case of an intermolecular reaction, the nucleophile and the electrophile must first come together from their initial random positions. This requires an increase in the order of the system, an entropically unfavorable process. In the case of an intramolecular reaction, the nucleophile is held in proximity to the electrophile by the connecting carbon chain. It takes a much smaller increase in the order of the system to position the nucleophile for reaction. In other words, the nucleophile is much closer to the electrophile at all times, and attaining the proper orientation required for the reaction is much more probable.

As mentioned earlier, three-, five-, and six-membered rings are preferred in intramolecular reactions. In the case of a three-membered ring, the increase in strain energy disfavors its formation; that is, it makes the enthalpy change in the reaction more positive (less favorable). However, the reaction centers are held so close that the entropy change for the reaction is quite favorable. In this case, entropy wins over enthalpy; three-membered rings are easily prepared in the laboratory, although they are often quite reactive. In contrast, the strain energy for four-membered rings is still large, whereas the entropy change is not as favorable, because the reaction centers are further apart. The enthalpy effect is larger than the entropy effect. As a result, four-membered rings are more difficult to prepare. For reactions that form five- and six-membered rings, the electrophile and nucleophile are even farther apart. However, because these rings are virtually strain free, there is no unfavorable enthalpy contribution. The entropy effect, although smaller, still enables five- and six-membered rings to be prepared readily in the laboratory. These rings are also the most common ones in naturally occurring compounds. Larger rings are less easily prepared because the entropy effect is no longer of much assistance.

PROBLEM 8.17

Show the products of these reactions. (Remember that acid–base reactions are usually much faster than nucleophilic substitution reactions.)

a) $Cl{-}CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH + {}^{-}OH \longrightarrow$

b) 

8.14 COMPETING REACTIONS

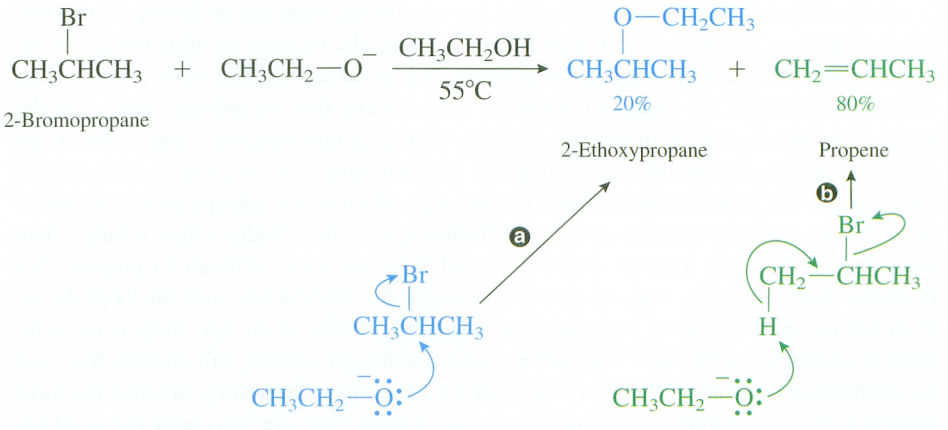
We have already seen that the S_N1 and S_N2 reactions may be in competition under certain circumstances. In addition, other reactions also compete with these two. If we are trying to prepare a specific compound, these competing reactions often result in a lower yield of the desired compound and may also cause purification problems.

An **elimination reaction,** in which the leaving group and a hydrogen are lost from adjacent carbons, resulting in the formation of a double bond between these two carbons, competes with both the S_N1 and S_N2 reactions. Figure 8.11 shows a reaction that produces both elimination and substitution products under S_N2 conditions. The competition occurs because the nucleophile is also a base. When it reacts as a base, it removes a proton from the carbon adjacent to the leaving group, resulting in the formation of the elimination product.

In the S_N1 mechansim, a competition between elimination and substitution also results from the ability of the nucleophile to act as a base. However, in this case the competition occurs at the carbocation stage of the reaction. Figure 8.12 shows an example. Elimination reactions are discussed in more detail in Chapter 9. Chapter 10 presents methods to minimize elimination when the substitution product is desired and methods to maximize elimination when the alkene is the desired product. For now it is important only to recognize that eliminations may decrease the yields in substitution reactions.

Figure 8.11

COMPETITION BETWEEN S_N2 AND ELIMINATION REACTIONS.



a Ethoxide ion acts as a nucleophile, attacking the carbon, resulting in the formation of the S_N2 product.

b Ethoxide ion acts as a base, removing a proton to give the elimination product. The by-product is ethanol.

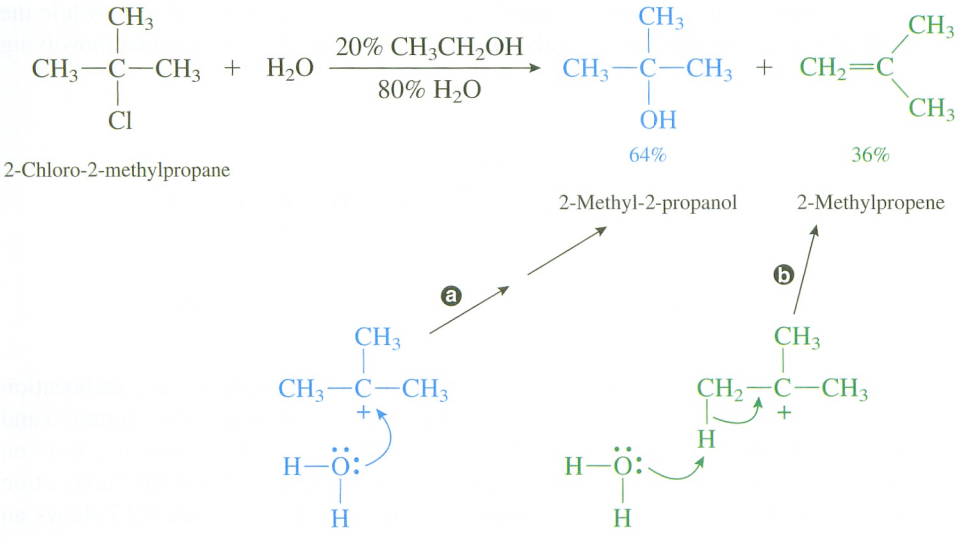


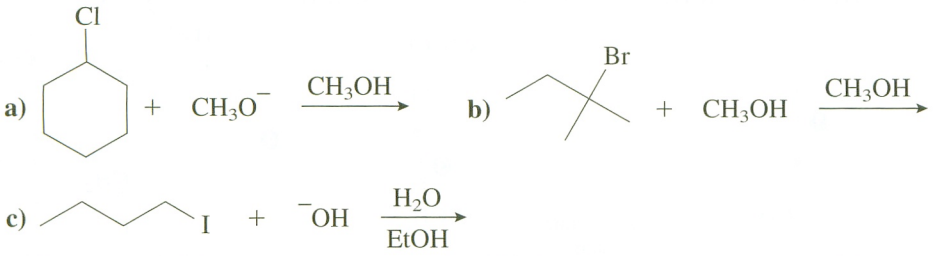
Figure 8.12
COMPETITION BETWEEN S_N1 AND ELIMINATION REACTIONS.

a Water acts as a nucleophile, bonding to the cationic carbon to give, after the loss of a proton, the substitution product.

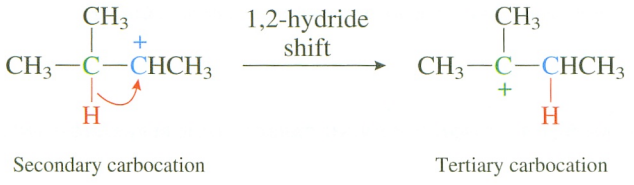
b Water acts as a base, removing a proton from the carbon adjacent to the cationic carbon to give the elimination product.

PROBLEM 8.18

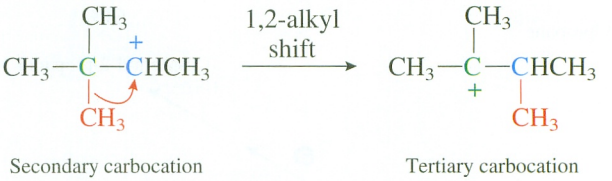
Show both the substitution and elimination products that are formed in these reactions:



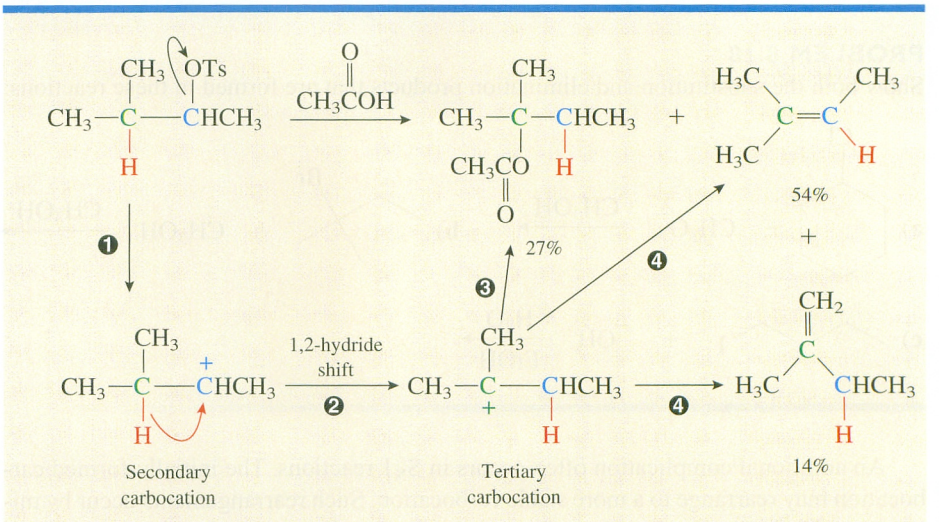
An additional complication often occurs in S_N1 reactions. The initially formed carbocation may rearrange to a more stable carbocation. Such rearrangements occur by migration of a hydrogen, or other group, with its bonding pair of electrons from an *adjacent* carbon to the positively charged carbon. Because the hydrogen moves as $H:^-$ (which is named **hydride**) between atoms that are adjacent, the process is termed a 1,2-hydride shift. A similar migration of an alkyl group (a 1,2-alkyl shift) can also occur. An example of a rearrangement involving a 1,2-hydride shift is



This rearrangement is favorable because the initial carbocation is secondary while the product is a more stable tertiary carbocation. An example of a rearrangement involving a 1,2-alkyl shift is



The change from the secondary carbocation to the more stable tertiary carbocation again makes this rearrangement favorable. These rearrangements are very common and invariably occur if the rearranged carbocation is more stable. Therefore, if a reaction that proceeds through a carbocation intermediate is being considered, the carbocation must always be examined for the possibility of rearrangement. Figure 8.13 shows an S_N1 reaction in which both the substitution and the elimination products are produced from a rearranged carbocation.



❶ The carbocation formed initially in this reaction is secondary. Only a very small amount of product is formed from this cation.

❷ Instead, it rearranges to a more stable tertiary carbocation by a 1,2-hydride shift.

❸ The tertiary carbocation produces 27% of the substitution product (S_N1) and ❹ 68% of the elimination products. In this case there are two possible elimination products, depending on which adjacent carbon loses the hydrogen. Situations like this are discussed in more detail in Chapter 9.

Figure 8.13

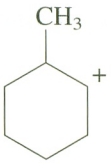
MECHANISM OF AN S_N1 REACTION INVOLVING CARBOCATION REARRANGEMENT.

PROBLEM 8.19

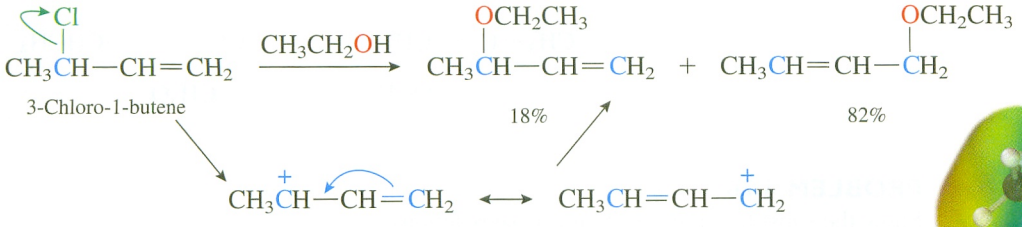
Show the rearranged carbocations that are expected from these carbocations:

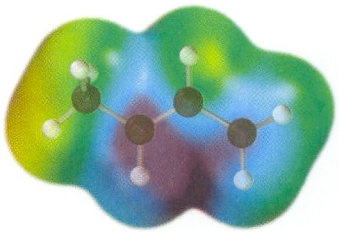
a)

b) $CH_3CHCHCH_2CH_3$ (with CH_3 above the first CH and + below the first CH)

c) 

Finally, it is important to recognize that an S_N1 reaction that forms an allylic carbocation often provides more than one site at which the nucleophile can bond. The nucleophile may bond to either of the carbons that bear the positive charges in the resonance structures. If the allylic cation is not symmetrical, this will result in the formation of two products: one "normal" and one "rearranged." An example of such an "allylic rearrangement" is



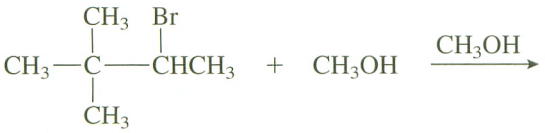


Allylic carbocation

Note that this "rearrangement" is fundamentally different from the previously described carbocation rearrangements. The allyl carbocation has partial positive charge located on two carbons, both of which are expected to react with the nucleophile. One resonance structure does not "rearrange" to the other. It would be quite surprising if two products were not produced from such a resonance stabilized carbocation.

PRACTICE PROBLEM 8.5

Show the substitution products for this reaction:

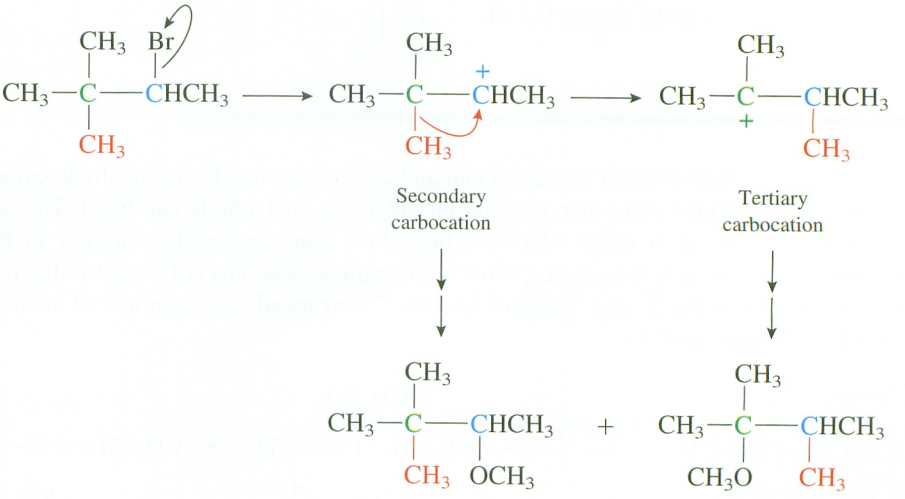


Strategy

Whenever an S_N1 reaction is encountered, it is important to examine the carbocation for the possibility of rearrangement. Rearrangement will occur if the carbon adjacent to the electrophilic carbon is bonded to more carbon groups than the electrophilic carbon. In such cases, at least part of the product results from the carbocation formed by migration of a hydrogen or an alkyl group from the adjacent C to the electrophilic C.

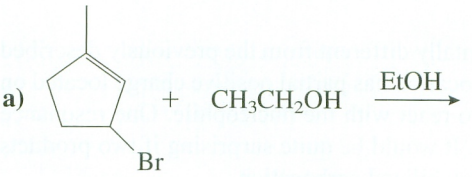
Solution

The leaving group (Br) is on a secondary carbon. The reaction involves a poor nucleophile (CH_3OH) and a polar solvent (CH_3OH), so it follows an S_N1 mechanism. The initial carbocation is secondary and can rearrange to a tertiary carbocation by migration of a methyl group.



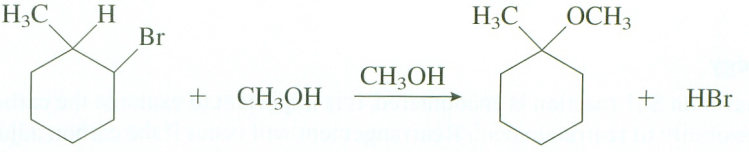
PROBLEM 8.20

Show the substitution products for these reactions:



PROBLEM 8.21

a) Show all of the steps in the mechanism for this reaction. Don't forget to use curved arrows to show the movement of electrons in each step of the mechanism.



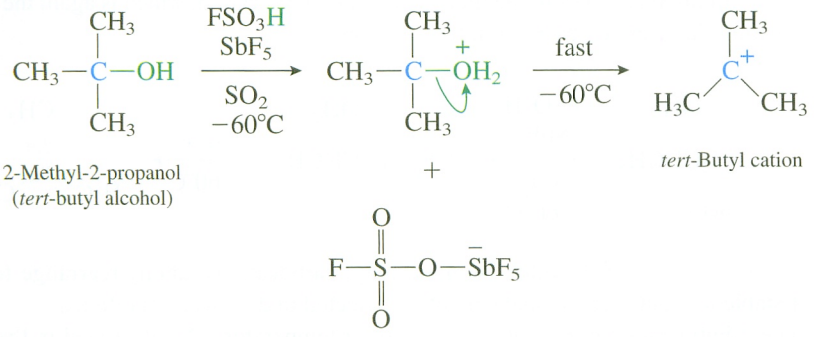
b) Show a free energy versus reaction progress diagram for this reaction.

Focus On

Carbocation Rearrangements in Superacids

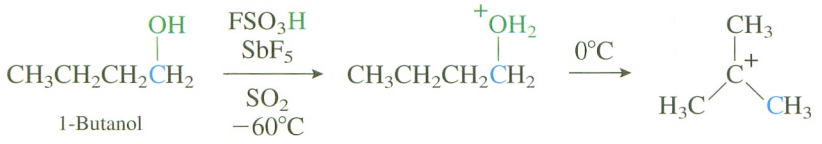
Normally, carbocations are encountered as transient intermediates along the pathway of reactions such as the S_N1 substitution. However, under conditions in which no nucleophiles or bases are available to react with them, carbocations can have significant lifetimes. Because superacids are very weak nucleophiles (see Section 4.10) and are quite polar, they provide an environment in which carbocations have lifetimes long enough to allow them to be studied by a variety of instrumental techniques.

As an example, the *tert*-butyl cation can be generated by treating 2-methyl-2-propanol (*tert*-butyl alcohol) with the superacid FSO_3H/SbF_5 in liquid sulfur dioxide as the solvent. The reaction is shown in the following equation:



First, the oxygen is protonated to make it a better leaving group. Then water leaves to produce the *tert*-butyl cation. This step is very fast, even at −60°C, so the carbocation is the only product that can be detected as soon as the alcohol is added to the superacid medium. Because there is no nucleophile for the carbocation to react with (the H_2O generated in the reaction is protonated by the strong acid to form H_3O^+), its lifetime under these conditions is quite long, and it can be studied by a variety of techniques.

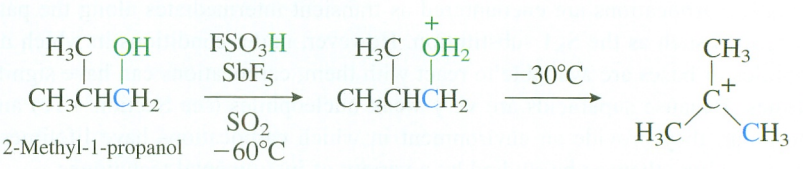
As we have seen, carbocations rearrange even under the conditions of the S_N1 reaction, in which their lifetimes are extremely short and rearrangement must compete with the fast reaction with a nucleophile. Therefore, in superacid solution, in which their lifetimes are much longer, it is not surprising that carbocations undergo extensive rearrangements. Usually, such rearrangements occur until a tertiary carbocation is formed. For example, consider the case in which 1-butanol is dissolved in superacid solution:



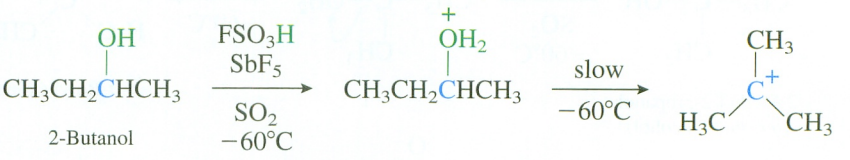
At −60°C, the protonated alcohol is formed but water does not leave because the primary carbocation that would be formed is too unstable. When the temperature is

Continued

raised to 0°C, water leaves but the carbocation rearranges rapidly to the more stable *tert*-butyl cation, which is the only carbocation that can be observed. The other two isomeric 4-carbon alcohols behave similarly. At −60°C, 2-methyl-1-propanol is protonated but water does not leave because the carbocation that would be formed is primary. When the temperature of the solution is raised to −30°C, water leaves and the *tert*-butyl cation is again produced by rapid rearrangements.

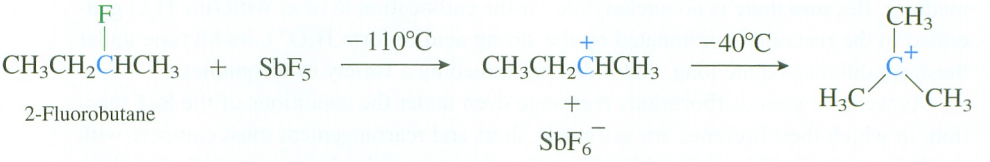


When 2-butanol is treated under the same conditions, the protonated alcohol is again the first species that is observed. However, because a more stable secondary carbocation is produced initially, water slowly leaves even at −60°C. The secondary carbocation rapidly rearranges to the more stable *tert*-butyl cation, which is again the only carbocation that can be observed in the solution.



In summary, all of the other isomeric butyl carbocations rapidly rearrange to the most stable *tert*-butyl cation and cannot be detected under these conditions.

The 2-butyl cation can be observed at lower temperature. As illustrated in the following equation, it is formed by the reaction of 2-fluorobutane with SbF_5 at −110°C. When the temperature of the solution is raised to −40°C, rearrangement to the *tert*-butyl cation occurs.



Overall, these and related experiments help confirm the existence of carbocations and show that the activation energies for their rearrangements must be small in most cases because the rearrangements occur rapidly at rather low temperatures. In addition, it is readily apparent that a tertiary carbocation is considerably more stable than are primary or secondary carbocations.

Review of Mastery Goals

After completing this chapter, you should be able to:

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- Write mechanisms for the S_N1 and S_N2 reactions. (Problems 8.29, 8.35, 8.43, 8.44, and 8.45)
- Recognize the various nucleophiles and leaving groups and understand the factors that control their reactivities. (Problems 8.31, 8.32, 8.33, 8.41, 8.42, and 8.52)
- Understand the factors that control the rates of these reactions, such as steric effects, carbocation stabilities, the nucleophile, the leaving group, and solvent effects. (Problems 8.22, 8.23, 8.24, 8.25, 8.34, 8.39, 8.55, 8.59, and 8.60)
- Be able to use these factors to predict whether a particular reaction will proceed by an S_N1 or an S_N2 mechanism and to predict what effect a change in reaction conditions will have on the reaction rate. (Problems 8.28, 8.36, 8.37, and 8.38)
- Show the products of any substitution reaction. (Problems 8.26, 8.27, 8.30, 8.40, 8.50, 8.51, and 8.56)
- Show the stereochemistry of the products. (Problems 8.27, 8.56, 8.57, and 8.58)
- Recognize when a carbocation rearrangement is likely to occur and show the products expected from the rearrangement. (Problems 8.47 and 8.48)
- Show the structures of the products that result from the elimination reactions that compete with the substitution reactions. (Problem 8.46)

Visual Summary of Key Reactions

The importance of identifying the electrophile and the nucleophile in organic reactions cannot be overemphasized. The electrophile is usually a carbon bonded to an electronegative element so that the carbon is electron deficient. The nucleophile most often contains an atom with an unshared pair of electrons, a Lewis base. In this chapter the electrophilic carbon is the one bonded to a leaving group. A few nucleophiles have been presented, but many more will be discussed in Chapter 10. Later chapters will introduce new electrophiles or new nucleophiles, but the new reactions always involve the nucleophile forming a bond to the electrophile.

Table 8.6 provides a summary of the most important features of the S_N1 and S_N2 reactions.

Table 8.6 Summary of the S_N1 and S_N2 Reactions

	S_N1	S_N2
Mechanism	Two step R—L ⟶ R^+ ⟶ R—Nu	One step R—L + Nu^- ⟶ R—Nu + L^-
Kinetics	First-order rate = k[R—L]	Second-order rate = k[R—L][Nu^-]
Effects of Nucleophile	No effect on rate (favored by weaker nucleophiles because S_N2 is slower)	Stronger nucleophiles cause faster rate
Effect of Carbon Structure	Tertiary > secondary Resonance stabilization of R^+ important	Methyl > primary > secondary
Stereochemistry	Racemization (possibly excess inversion)	Inversion
Effect of Solvent	Favored by polar solvents	Favored by aprotic solvents
Competing Reactions	Elimination, rearrangement	Elimination

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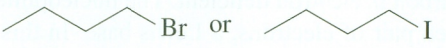
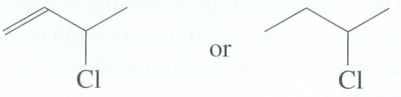
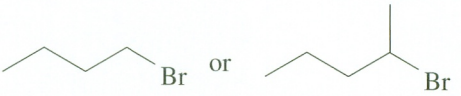
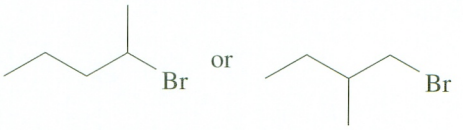
Additional Problems

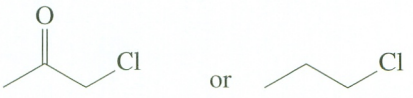
8.22 Which of these compounds would have a faster rate of S_N2 reaction?

a) 

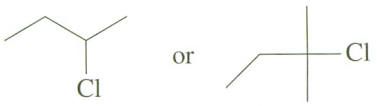
b) 

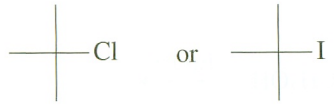
c) 

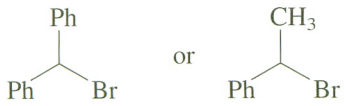
d) 

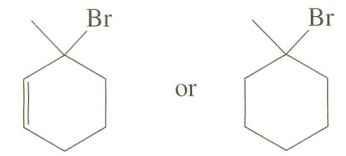
e) 

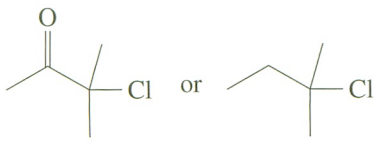
8.23 Which of these compounds would have a faster rate of S_N1 reaction?

a) 

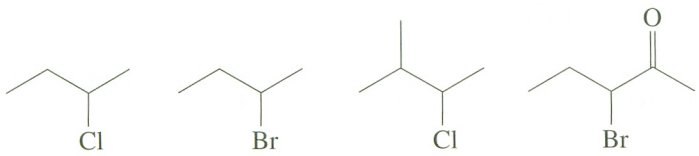
b) 

c) 

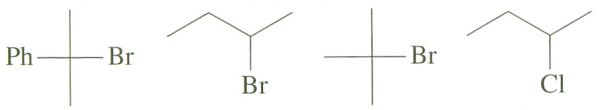
d) 

e) 

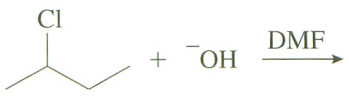
8.24 Arrange these compounds in order of increasing S_N2 reaction rate:

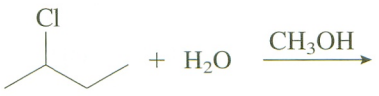


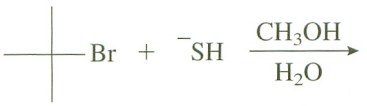
8.25 Arrange these compounds in order of increasing S_N1 reaction rate:



8.26 Show the products of these reactions and explain whether each would follow an S_N1 or an S_N2 mechanism:

a) 

b) 

c) 

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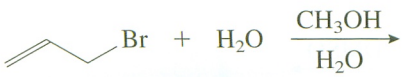
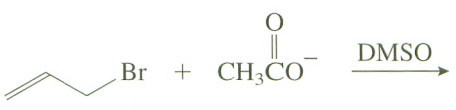
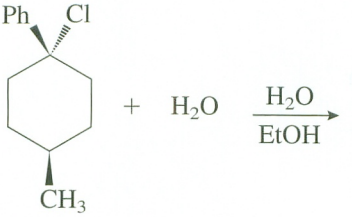
e) 

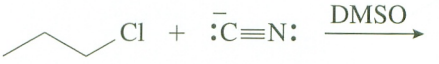
f) 

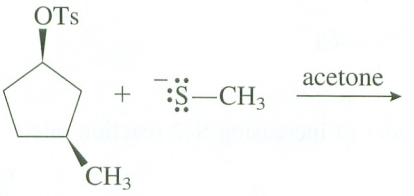
8.27 Show the substitution products for these reactions. Don't forget to show the stereochemistry of the product, where appropriate.

a)

b)

c) 

d) 

e) 

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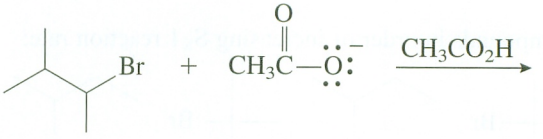
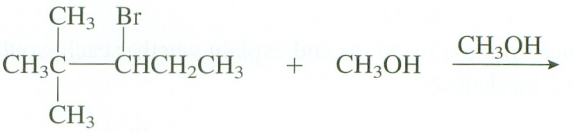
g) 

h) 

i)

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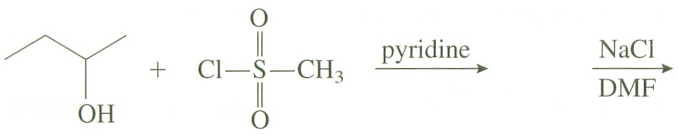
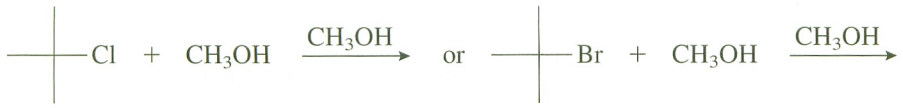
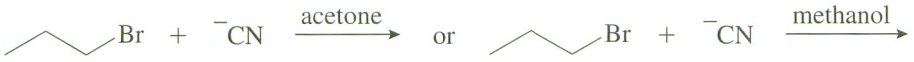
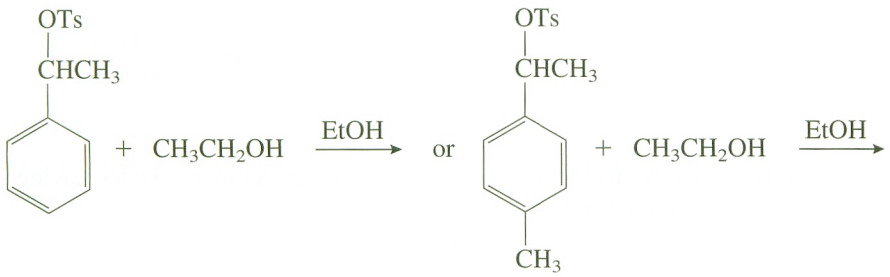
l) 

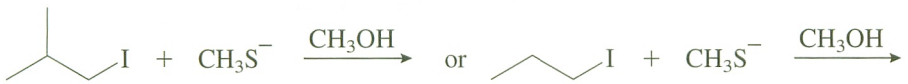
m) $CH_3CH_2CH_2CH_2Br + NaI \xrightarrow{\text{acetone}}$

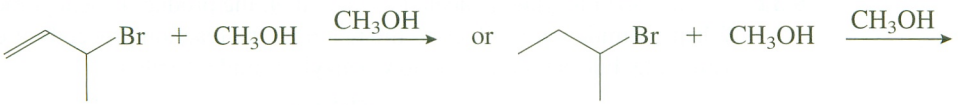
8.28 Explain whether each pair of reactions should follow an S_N1 or an S_N2 mechanism. Then explain which member of the pair should proceed at a faster rate.

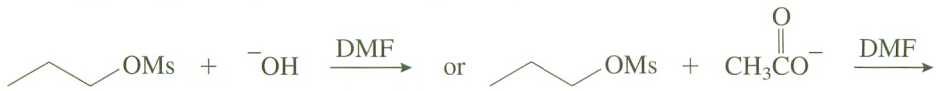
a) 

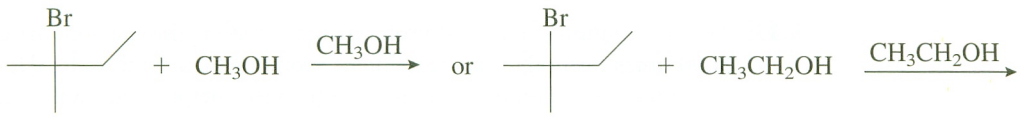
b) 

c) 

d) 

e) 

f) 

g) 

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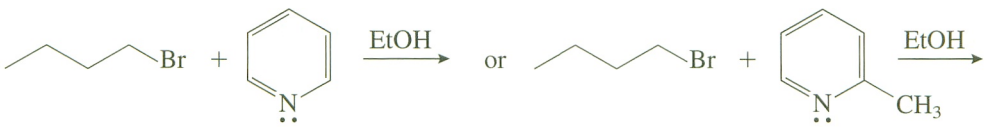
i) 

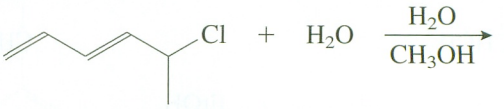
8.29 Show all of the steps in the mechanisms of these reactions:

a) $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-Br + CH_3CH_2OH \xrightarrow{EtOH} CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-OCH_2CH_3 + CH_3CH_2\overset{+}{O}H_2\ \overset{-}{Br}$

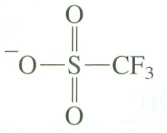
b) $CH_3CH_2CH_2\underset{Cl}{\underset{|}{C}}H_2 + CH_3O^- \xrightarrow{DMSO} CH_3CH_2CH_2\underset{OCH_3}{\underset{|}{C}}H_2 + Cl^-$

c) $CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}CH_3 + \underset{\displaystyle Br^-}{H_3O^+} \xrightarrow{H_2O} CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle Br}{\overset{|}{\underset{|}{C}}}}CH_3 + 2\,H_2O$

8.30 This reaction gives three substitution products (not counting *E/Z* isomers). Show the structures of these products and show the mechanism for their formation:

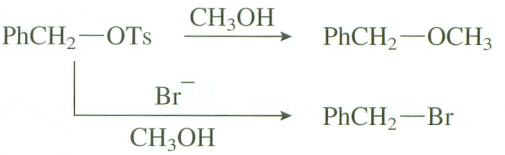


8.31 Explain why the trifluoromethanesulfonate anion is a better leaving group than the mesylate anion.



Trifluoromethanesulfonate anion

8.32 When benzyl tosylate is heated in methanol, the product is benzyl methyl ether. When bromide ion is added to the reaction, the reaction proceeds at exactly the same rate, but the product is now benzyl bromide. Explain.

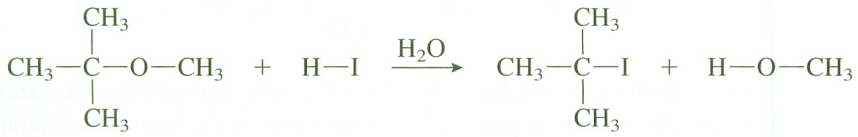


8.33 The substitution reaction of bromomethane with hydroxide ion proceeds about 5000 times faster than the reaction of bromomethane with water. However, the substitution reaction of 2-bromo-2-methylpropane proceeds at the same rate with both of these nucleophiles. Explain.

8.34 Explain why this primary halide reacts very rapidly under conditions that are favorable for the S_N1 mechanism:

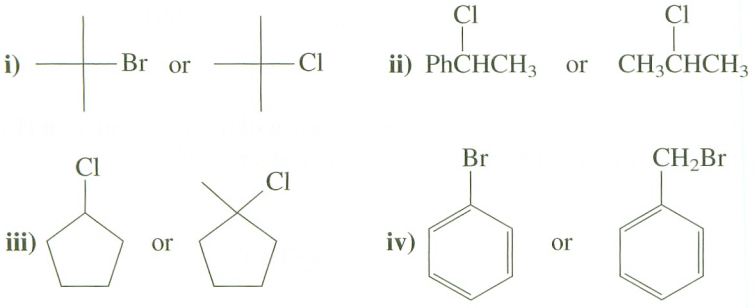
$$CH_3-O-CH_2-Cl$$

8.35 Ethers can be cleaved by treatment with strong acids. Show all of the steps in the mechanism for this reaction and explain why these products are formed rather than iodomethane and 2-methyl-2-butanol:



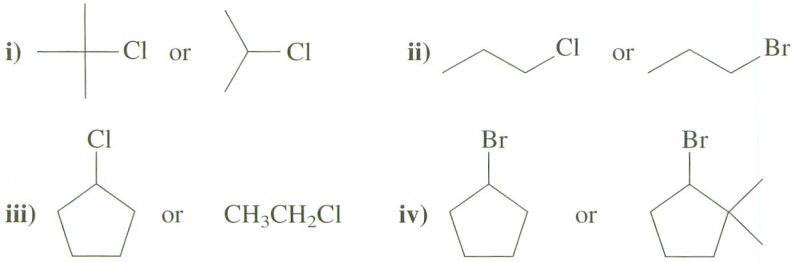
8.36 The reaction of a compound with silver nitrate in ethanol is used as a chemical test to determine if the compound is an alkyl halide. The formation of a precipitate of the silver halide constitutes a positive test.

a) Explain why these conditions favor the S_N1 mechanism.
b) Which of these halides would give a precipitate more rapidly when reacted with $AgNO_3$ in ethanol?



8.37 The reaction of an alkyl chloride (or bromide) with sodium iodide in acetone proceeds according to the following equation:

Sodium iodide is soluble in acetone, whereas both sodium chloride and sodium bromide are insoluble, so the appearance of a precipitate is a positive test for the presence of an alkyl chloride or bromide.
a) Explain why these conditions favor the S_N2 mechanism.
b) Which of these halides would give a precipitate more rapidly when reacted with NaI in acetone?



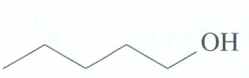
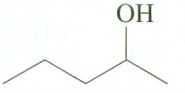
8.38 The Lucas test is used to check for the presence of an alcohol functional group in an unknown compound. The test reaction is shown in the following equation:

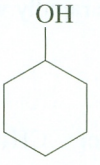
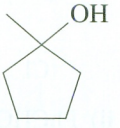
$$R{-}OH + HCl \xrightarrow[H_2O]{ZnCl_2} R{-}Cl + H_2O$$

Smaller alcohols are soluble in the strongly acidic solution, but the corresponding chlorides are not. A positive test is indicated by the formation of an insoluble layer of the alkyl chloride.

a) Explain why the reaction conditions favor an S_N1 mechanism.

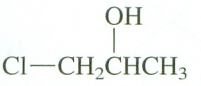
b) Which of these alcohols reacts more rapidly with HCl and $ZnCl_2$ in H_2O?

i)  or 

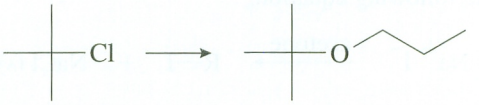
ii)  or 

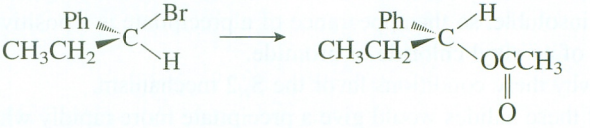
iii) or

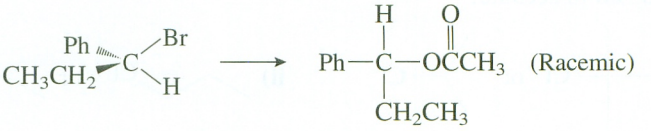
8.39 Explain why this secondary alcohol reacts with HCl and $ZnCl_2$ in H_2O at about the same rate as a primary alcohol (see problem 8.38):



8.40 What reagent and solvent would you use to carry out the following transformations?

a) 

b) 

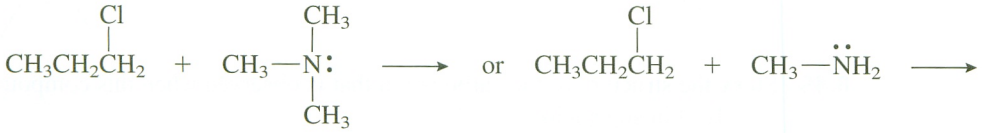
c) 

d)

e)

8.41 In most cases, RO^- cannot act as a leaving group in nucleophilic substitution reactions. Explain why the following reaction does occur:

8.42 Explain which of these reactions would have the faster rate:

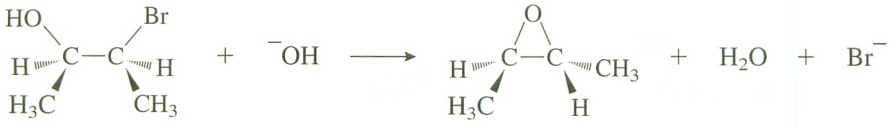


8.43 Heating ethanol with sulfuric acid is one method used for the preparation of diethyl ether. Show all of the steps in the mechanism for this reaction:

$$2\ CH_3CH_2OH \xrightarrow{H_2SO_4} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O$$

8.44 When an aqueous solution of (*R*)-2-butanol is treated with a catalytic amount of sulfuric acid, slow racemization of the alcohol occurs. Show all of the steps in the mechanism for this process.

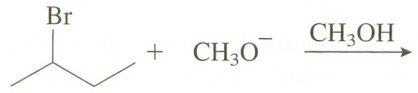
8.45 Show all of the steps in the mechanism and explain the stereochemistry for this reaction:



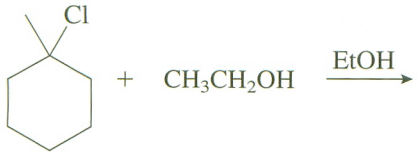
8.46 Show both the substitution and elimination products that would be formed in these reactions:

a)

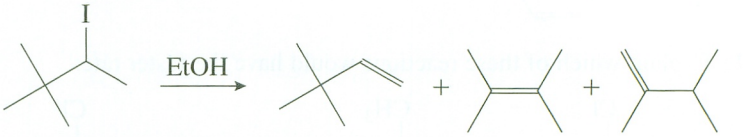
b)



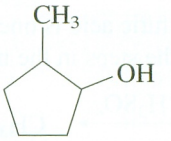
c)



8.47 The reaction of 3-iodo-2,2-dimethylbutane with ethanol gives three elimination products in addition to two substitution products as shown in the following equation. Show all the steps in the mechanism for the formation of the elimination products. Show the structures of the substitution products.



8.48 Show the structure of the carbocation that is observed when this compound is dissolved in superacid:

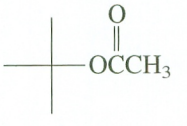


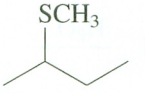
8.49 How much is the reaction rate for these reactions increased or decreased if the concentration of hydroxide ion is doubled? if the concentrations of both the alkyl chloride and hydroxide ion are halved?

a) $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}H_2 + {}^{-}OH \xrightarrow{H_2O}$

b) $CH_3\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-Cl + {}^{-}OH \xrightarrow{H_2O}$

8.50 Show how these compounds could be prepared from alkyl halides:

a) 

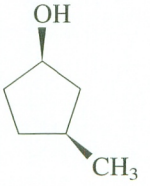
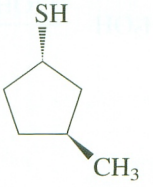
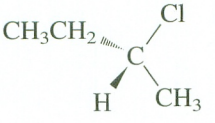
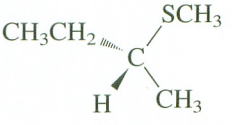
b) 

Two methods

c)

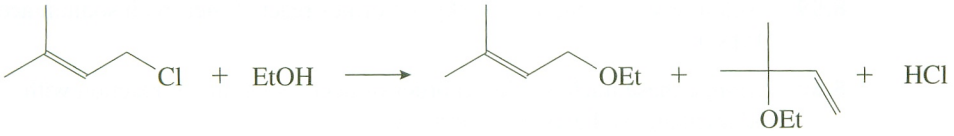
Two methods

8.51 Show how these products could be synthesized from the indicated starting material. More than one step may be necessary. Make sure that the product has the stereochemistry shown.

	Starting material	Product
a)		
b)		

8.52 Cyanide anion has two potential nucleophilic sites: the carbon and the nitrogen. Explain which site is expected to be the stronger nucleophile.

8.53 This S_N1 reaction gives the mixture of products shown. Show the structure of the carbocation formed in this reaction and explain what factor favors the reaction of the nucleophile at the primary carbon and what factor favors reaction at the tertiary carbon.



8.54 The rearrangements of both the 1-butyl and 2-butyl carbocations to the *tert*-butyl carbocation occur rapidly in superacid solution. Both of these rearrangements proceed through several steps and must involve an unfavorable secondary carbocation to primary carbocation rearrangement. Show the steps in the rearrangement of the 1-butyl carbocation to the *tert*-butyl carbocation.

8.55 The two nitrogens of the following dipeptide have very different reactivities as nucleophiles. Explain which nitrogen is the better nucleophile.

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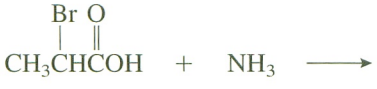
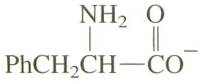
8.56 Amino acids can be prepared (as their conjugate bases) by the reaction of a bromine substituted carboxylic acid with excess ammonia.

a) The conjugate base of the amino acid alanine is formed in the following reaction. Show the structure of the product and explain why an excess of ammonia is required. Explain which mechanism the reaction follows.



BioLink

b) Show how a similar reaction could be used to prepare the conjugate base of the amino acid phenylalanine.



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8.57 Explain which of the two acetate esters, product 1 or product 2, is formed when the alkyl chloride is reacted with sodium acetate in DMSO.

8.58 Explain which of the two methyl ethers, product 1 or product 2, is formed when the alkyl chloride is heated in methanol.

8.59 Explain which of these two alkyl chlorides reacts faster with sodium acetate in DMSO.

8.60 Arrange these nucleophiles in order of decreasing rate of reaction with iodomethane and explain your answer.

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